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Integrated Science Assessment for Particulate Matter

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PREFACE

The Preface to the Integrated Science Assessment for Particulate Matter (PM ISA) outlines the legislative requirements of a National Ambient Air Quality Standard (NAAQS) review and the history of the PM NAAQS. This information provides an understanding of the function of the ISA, and in terms of providing a starting point for this PM ISA, presents the basis for the decisions that supported the previous PM NAAQS review. In addition, the Preface details the purpose of the ISA as well as specific issues pertinent to the evaluation of the scientific evidence that takes place within this ISA, including the scope of the ISA and discipline specific decisions that governed parts of the review.

P.1 Legislative Requirements for the Review of the National Ambient Air Quality Standards

Two sections of the Clean Air Act (CAA) govern the establishment, review, and revision of the National Ambient Air Quality Standards (NAAQS). Section 108 [42 U.S. Code (U.S.C.) 7408] directs the Administrator to identify and list certain air pollutants and then to issue air quality criteria for those pollutants. The Administrator is to list those air pollutants that in their "judgment, cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare," "the presence of which in the ambient air results from numerous or diverse mobile or stationary sources," and "for which … [the Administrator] plans to issue air quality criteria …" [42 U.S.C. 7408(a)(1); (CAA, 1990a)]. Air quality criteria are intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare, which may be expected from the presence of [a] pollutant in the ambient air …" [42 U.S.C. 7408(b)]. Section 109 [42 U.S.C. 7409; (CAA, 1990b)] directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants for which air quality criteria are issued. Section 109(b)(1) defines a primary standard as one "the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."[4] A secondary standard, as defined in Section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the judgment of the Administrator, based on such criteria, is requisite to protect

[4] The legislative history of Section 109 indicates that a primary standard is to be set at "… the maximum permissible ambient air level…which will protect the health of any [sensitive] group of the population," and that for this purpose "reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group" S. Rep. No. 91:1196, 91st Cong., 2d Sess. 10 (1970).

the public welfare from any known or anticipated adverse effects associated with the presence of [the] air pollutant in the ambient air."[5]

The requirement that primary standards provide an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It was also intended to provide a reasonable degree of protection against hazards that research has not yet identified.[6] Both kinds of uncertainty are components of the risk associated with pollution at levels below those at which human health effects can be said to occur with reasonable scientific certainty. Thus, in selecting primary standards that provide an adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree. The CAA does not require the Administrator to establish a primary NAAQS at a zero-risk level or at background concentration levels, but rather at a level that reduces risk sufficiently so as to protect public health with an adequate margin of safety.[7] In so doing, protection is provided for both the population as a whole and those groups and lifestages potentially at increased risk for health effects from exposure to the air pollutant for which each NAAQS is set.

In addressing the requirement for an adequate margin of safety, the U.S. Environmental Protection Agency (U.S. EPA) considers such factors as the nature and severity of the health effects involved, the size of the sensitive group(s), and the kind and degree of the uncertainties. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment.[8]

In setting standards that are "requisite" to protect public health and welfare as provided in Section 109(b), the U.S. EPA's task is to establish standards that are neither more nor less stringent than necessary for these purposes. In so doing, the U.S. EPA may not consider the costs of implementing the standards.[9] Likewise, "[a]ttainability and technological feasibility are not relevant considerations in the promulgation of national ambient air quality standards."[10]

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[5] Section 302(h) of the Act [42 U.S.C. 7602(h)] provides that all language referring to effects on welfare includes, but is not limited to, "effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being…" (CAA, 2005).

[6] See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 [District of Columbia Circuit (D.C. Cir.) 1980]; *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981); *American Farm Bureau Federation v. EPA*, 559 F. 3d 512, 533 (D.C. Cir. 2009); *Association of Battery Recyclers v. EPA*, 604 F. 3d 613, 617–18 (D.C. Cir. 2010).

[7] See *Lead Industries v. EPA*, 647 F.2d at 1156 n.51; *Mississippi v. EPA*, 744 F. 3d 1334, 1339, 1351, 1353 (D.C. Cir. 2013).

[8] See *Lead Industries Association v. EPA,* 647 F.2d at 1161–62; *Mississippi v. EPA,* 744 F. 3d at 1353.

[9] See generally, *Whitman v. American Trucking Associations*, 531 U.S. 457, 465–472, 475–476 (2001).

[10] See *American Petroleum Institute v. Costle,* 665 F. 2d at 1185.

Section 109(d)(1) requires that "not later than December 31, 1980, and at 5-year intervals thereafter, the Administrator shall complete a thorough review of the criteria published under Section 108 and the national ambient air quality standards…and shall make such revisions in such criteria and standards and promulgate such new standards as may be appropriate…." Section 109(d)(2) requires that an independent scientific review committee "shall complete a review of the criteria…and the national primary and secondary ambient air quality standards…and shall recommend to the Administrator any new…standards and revisions of existing criteria and standards as may be appropriate…." Since the early 1980s, this independent review function has been performed by the Clean Air Scientific Advisory Committee (CASAC).[11]

P.1.1. Overview and History of the Reviews of the Primary and Secondary National Ambient Air Quality Standard for Particulate Matter

NAAQS are defined by four basic elements: indicator, averaging time, level, and form. The indicator defines the pollutant to be measured in the ambient air for the purpose of determining compliance with the standard. The averaging time defines the time period over which air quality measurements are to be obtained and averaged or cumulated, considering evidence of effects associated with various time periods of exposure. The level of a standard defines the air quality concentration used (i.e., an ambient concentration of the indicator pollutant) in determining whether the standard is achieved. The form of the standard defines the air quality statistic that is compared to the level of the standard in determining whether an area attains the standard. For example, the form of the current primary annual fine particulate matter ($PM_{2.5}$) standard is the annual mean averaged over 3 years. The Administrator considers these four elements collectively in evaluating the protection to public health provided by the primary NAAQS.

Particulate matter (PM) is the generic term for a broad class of chemically and physically diverse substances that exist as discrete particles (liquid droplets or solids) over a wide range of sizes. Particles originate from a variety of anthropogenic stationary and mobile sources, as well as from natural sources. Particles may be emitted directly or formed in the atmosphere by transformations of gaseous emissions such as sulfur oxides (SO_X), oxides of nitrogen (NO_X), ammonia (NH_3) and volatile organic compounds (VOC). Examples of secondary particle formation include: (1) the conversion of SO_2 to sulfuric acid (H_2SO_4) vapor that nucleates new particles or condenses on existing particles and further reacts with NH_3 to form various inorganic salts (e.g., ammonium sulfate, $[NH_4]_2SO_4$, or ammonium bisulfate, NH_4HSO_4); (2) the conversion of nitrogen dioxide (NO_2) to nitric acid (HNO_3) vapor that condenses onto existing particles and reacts further with ammonia to form ammonium nitrate (NH_4NO_3); and (3) reactions

[11] Lists of CASAC members and of members of the CASAC Augmented for the Particulate Matter Panel are available at: https://yosemite.epa.gov/sab/sabpeople.nsf/WebCommitteesSubcommittees/CASAC%20Particulate%20Matter%20Review%20Panel%20(2015-2018).

involving gaseous VOC yielding organic compounds with low vapor pressures that nucleate or condense on existing particles to form secondary organic particulate matter (SOPM) (U.S. EPA, 2004). The chemical and physical properties of PM vary greatly with time, region, meteorology, and source category, thus complicating the assessment of health and welfare effects. These reviews are briefly described below, and further details are provided in the Integrated Review Plan (U.S. EPA, 2016).

The U.S. EPA first established NAAQS for PM in 1971 (36 FR 8186, April 30, 1971), based on the original criteria document (NAPCA, 1969).[12] The federal reference method (FRM) specified for determining attainment of the original standards was the high-volume sampler, which collects PM up to a nominal size of 25 to 45 micrometers (μm) (referred to as total suspended particulates or TSP). The primary standards were at 260 $\mu g/m^3$, 24-hour average, not to be exceeded more than once per year, and 75 $\mu g/m^3$, annual geometric mean. The secondary standards were 150 $\mu g/m^3$, 24-hour average, not to be exceeded more than once per year, and 60 $\mu g/m^3$, annual geometric mean. Since then, the Agency has completed multiple reviews of the air quality criteria and standards, as summarized in Table P-1.

Table P-1 History of the National Ambient Air Quality Standards for particulate matter, 1971–2012.

Final Rule/Decision	Indicator	Averaging Time	Level	Form
1971 36 FR 8186 Apr 30, 1971	TSP	24 h	260 $\mu g/m^3$ (primary) 150 $\mu g/m^3$ (secondary)	Not to be exceeded more than once per year
		Annual	75 $\mu g/m^3$ (primary) 60 $\mu g/m^3$ (secondary)	Annual geometric mean
1987 52 FR 24634 Jul 1, 1987	PM_{10}	24 h	150 $\mu g/m^3$	Not to be exceeded more than once per year on average over a 3-yr period
		Annual	50 $\mu g/m^3$	Annual arithmetic mean, averaged over 3 yr

[12] Prior to the review initiated in 2007 (see below), the AQCD provided the scientific basis for the NAAQS.

Table P-1 (Continued): History of the National Ambient Air Quality Standards for particulate matter, 1971–2012.

Final Rule/Decision	Indicator	Averaging Time	Level	Form
1997 62 FR 38652 Jul 18, 1997	$PM_{2.5}$	24 h	65 µg/m^3	98th percentile, averaged over 3 yr
		Annual	15 µg/m^3	Annual arithmetic mean, averaged over 3 yr[a]
	PM_{10}	24 h	150 µg/m^3	Initially promulgated 99th percentile, averaged over 3 yr; when 1997 standards were vacated in 1999, the form of 1987 standards remained in place (not to be exceeded more than once per yr on average over a 3-yr period)
		Annual	50 µg/m^3	Annual arithmetic mean, averaged over 3 yr
2006 71 FR 61144 Oct 17, 2006	$PM_{2.5}$	24 h	35 µg/m^3	98th percentile, averaged over 3 yr
		Annual	15 µg/m^3	Annual arithmetic mean, averaged over 3 yr[a]
	PM_{10}	24 h	150 µg/m^3	Not to be exceeded more than once per yr on average over a 3-yr period
2012 78 FR 3085 Jan 15, 2013	$PM_{2.5}$	24 h	35 µg/m^3	98th percentile, averaged over 3-yr[c]
		Annual	12 µg/m^3 (primary) 15 µg/m^3 (secondary)	Annual arithmetic mean, averaged over 3-yr[b]
	PM_{10}[d]	24 h	150 µg/m^3	Not to be exceeded more than once per year on average over 3-yr

TSP = total suspended particulates.

[a]The level of the 1997 annual $PM_{2.5}$ standard was to be compared to measurements made at the community-oriented monitoring site recording the highest level, or, if specific constraints were met, measurements from multiple community-oriented monitoring sites could be averaged ("spatial averaging"). This approach was judged to be consistent with the short-term exposure epidemiologic studies on which the annual $PM_{2.5}$ standard was primarily based, in which air quality data were generally averaged across multiple monitors in an area or were taken from a single monitor that was selected to represent community-wide exposures, not localized "hot spots" (62 FR 38672). These criteria and constraints were intended to ensure that spatial averaging would not result in inequities in the level of protection afforded by the $PM_{2.5}$ standards. Community-oriented monitoring sites were specified to be consistent with the intent that a spatially averaged annual standard provide protection for persons living in smaller communities, as well as those in larger population centers.

[b]In the revisions to the PM NAAQS finalized in 2006, U.S. EPA tightened the constraints on the spatial averaging criteria by further limiting the conditions under which some areas may average measurements from multiple community-oriented monitors to determine compliance (71 FR 61165-61167, October 17, 2006).

[c]The level of the 24-h standard is defined as an integer (zero decimal places) as determined by rounding. For example, a 3-yr average 98th percentile concentration of 35.49 µg/m^3 would round to 35 µg/m^3 and thus meet the 24-h standard and a 3-yr average of 35.50µg/m^3 would round to 36 and, hence, violate the 24-h standard (40 CFR Part 50 Appendix N).

[d]The U.S. EPA revoked the annual PM_{10} NAAQS in 2006.

Note: When not specified, primary and secondary standards are identical.

In October 1979 (44 FR 56730, October 2, 1979), the U.S. EPA announced the first periodic review of the air quality criteria and NAAQS for PM. Revised primary and secondary standards were promulgated in 1987 (52 FR 24634, July 1, 1987). In the 1987 decision, the U.S. EPA changed the

indicator for particles from TSP to PM_{10}, in order to focus on the subset of inhalable particles small enough to penetrate to the thoracic region of the respiratory tract (including the tracheobronchial and alveolar regions), referred to as thoracic particles.[13] The level of the 24-hour standards (primary and secondary) was set at 150 $\mu g/m^3$, and the form was one expected exceedance per year, on average over 3 years. The level of the annual standards (primary and secondary) was set at 50 $\mu g/m^3$, and the form was annual arithmetic mean, averaged over 3 years.

In April 1994, the U.S. EPA announced its plans for the second periodic review of the air quality criteria and NAAQS for PM, and in 1997 the U.S. EPA promulgated revisions to the NAAQS (62 FR 38652, July 18, 1997). In the 1997 decision, the U.S. EPA determined that the fine and coarse fractions of PM_{10} should be considered separately. This determination was based on evidence that serious health effects were associated with short- and long-term exposures to fine particles in areas that met the existing PM_{10} standards. The U.S. EPA added new standards, using $PM_{2.5}$ as the indicator for fine particles (with $PM_{2.5}$ referring to particles with a nominal mean aerodynamic diameter less than or equal to 2.5 μm). These new standards were as follows: (1) an annual standard with a level of 15.0 $\mu g/m^3$, based on the 3-year average of annual arithmetic mean $PM_{2.5}$ concentrations from single or multiple community-oriented monitors;[14] and (2) a 24-hour standard with a level of 65 $\mu g/m^3$, based on the 3-year average of the 98th percentile of 24-hour $PM_{2.5}$ concentrations at each monitor within an area. Also, the U.S. EPA established a new reference method for the measurement of $PM_{2.5}$ in the ambient air and adopted rules for determining attainment of the new standards. To continue to address the coarse fraction of PM_{10} (referred to as thoracic coarse particles or $PM_{10-2.5}$; generally including particles with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm), the U.S. EPA retained the annual PM_{10} standard and revised the form of the 24-hour PM_{10} standard to be based on the 99th percentile of 24-hour PM_{10} concentrations at each monitor in an area. The U.S. EPA revised the secondary standards by setting them equal in all respects to the primary standards.

Following promulgation of the 1997 PM NAAQS, petitions for review were filed by a large number of parties, addressing a broad range of issues. In May 1999, the U.S. Court of Appeals for the District of Columbia Circuit (D.C. Circuit) upheld the U.S. EPA's decision to establish fine particle standards, holding that "the growing empirical evidence demonstrating a relationship between fine particle pollution and adverse health effects amply justifies establishment of new fine particle standards."

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[13] PM_{10} refers to particles with a nominal mean aerodynamic diameter less than or equal to 10 μm. More specifically, 10 μm is the aerodynamic diameter for which the efficiency of particle collection is 50%. Larger particles are not excluded altogether, but are collected with substantially decreasing efficiency while smaller particles are collected with increasing efficiency.

[14] The level of the 1997 annual $PM_{2.5}$ standard was to be compared to measurements made at the community-oriented monitoring site recording the highest concentration or, if specific constraints were met, measurements from multiple community-oriented monitoring sites could be averaged (i.e., "spatial averaging"). In the last review (completed in 2012) the U.S. EPA replaced the term "community-oriented" monitor with the term "area-wide" monitor. Area-wide monitors are those sited at the neighborhood scale or larger, as well as those monitors sited at micro-or middle scales that are representative of many such locations in the same CBSA (78 FR 3236, January 15, 2013).

American Trucking Associations v. U.S. EPA, 175 F. 3d 1027, 1055–56 (D.C. Cir. 1999). The D.C. Circuit also found "ample support" for the U.S. EPA's decision to regulate coarse particle pollution, but vacated the 1997 PM_{10} standards, concluding that the U.S. EPA had not provided a reasonable explanation justifying use of PM_{10} as an indicator for coarse particles. 175 F. 3d at 1054–55. Pursuant to the D.C. Circuit's decision, the U.S. EPA removed the vacated 1997 PM_{10} standards, and the pre-existing 1987 PM_{10} standards remained in place (65 FR 80776, December 22, 2000). The D.C. Circuit also upheld the U.S. EPA's determination not to establish more stringent secondary standards for fine particles to address effects on visibility. 175 F. 3d at 1027.

The D.C. Circuit also addressed more general issues related to the NAAQS, including issues related to the consideration of costs in setting NAAQS and the U.S. EPA's approach to establishing the levels of NAAQS. Regarding the cost issue, the court reaffirmed prior rulings holding that in setting NAAQS the U.S. EPA is "not permitted to consider the cost of implementing those standards." Id. at 1040-41. Regarding the levels of NAAQS, the court held that the U.S. EPA's approach to establishing the level of the standards in 1997 (i.e., both for PM and for the ozone NAAQS promulgated on the same day) effected "an unconstitutional delegation of legislative authority." Id. at 1034-40. Although the court stated that "the factors U.S. EPA uses in determining the degree of public health concern associated with different levels of ozone and PM are reasonable," it remanded the rule to the U.S. EPA, stating that when the U.S. EPA considers these factors for potential non-threshold pollutants "what U.S. EPA lacks is any determinate criterion for drawing lines" to determine where the standards should be set.

The D.C. Circuit's holding on the cost and constitutional issues were appealed to the U.S. Supreme Court. In February 2001, the Supreme Court issued a unanimous decision upholding the U.S. EPA's position on both the cost and constitutional issues. Whitman v. American Trucking Associations, 531 U.S. 457, 464, 475–76. On the constitutional issue, the Court held that the statutory requirement that NAAQS be "requisite" to protect public health with an adequate margin of safety sufficiently guided the U.S. EPA's discretion, affirming the U.S. EPA's approach of setting standards that are neither more nor less stringent than necessary.[15]

In October 1997, the U.S. EPA published its plans for the third periodic review of the air quality criteria and NAAQS for PM (62 FR 55201, October 23, 1997). After the CASAC and public review of several drafts, the U.S. EPA's NCEA finalized the Air Quality Criteria Document (AQCD) in October 2004 (U.S. EPA, 2004). The U.S. EPA's OAQPS finalized a Risk Assessment and Staff Paper in

[15] The Supreme Court remanded the case to the Court of Appeals for resolution of any remaining issues that had not been addressed in that court's earlier rulings. Id. at 475–76. In a March 2002 decision, the Court of Appeals rejected all remaining challenges to the standards, holding that the EPA's $PM_{2.5}$ standards were reasonably supported by the administrative record and were not "arbitrary and capricious" American Trucking Associations v. EPA, 283 F. 3d 355, 369-72 (D.C. Cir. 2002).

December of 2005 (Abt, 2005; U.S. EPA, 2005).[16] On December 20, 2005, the U.S. EPA announced its proposed decision to revise the NAAQS for PM, and solicited comment on a broad range of options (71 FR 2620, January 17, 2006). On September 21, 2006, the U.S. EPA announced its final decisions to revise the primary and secondary NAAQS for PM to provide increased protection of public health and welfare, respectively (71 FR 61144, October 17, 2006). With regard to the primary and secondary standards for fine particles, the U.S. EPA revised the level of the 24-hour $PM_{2.5}$ standards to 35 $\mu g/m^3$, retained the level of the annual $PM_{2.5}$ standards at 15.0 $\mu g/m^3$, and revised the form of the annual $PM_{2.5}$ standards by narrowing the constraints on the optional use of spatial averaging. For the primary and secondary standards for PM_{10}, the U.S. EPA retained the 24-hour standards, with levels at 150 $\mu g/m^3$, and revoked the annual standards.[17] The Administrator judged that the available evidence generally did not suggest a link between long-term exposure to existing ambient levels of coarse particles and health or welfare effects. In addition, a new reference method was added for the measurement of $PM_{10-2.5}$ in the ambient air, in order to provide a basis for approving federal equivalent methods (FEMs) and to promote the gathering of scientific data to support future reviews of the PM NAAQS.

Several parties filed petitions for review following promulgation of the revised PM NAAQS in 2006. These petitions addressed the following issues: (1) selecting the level of the primary annual $PM_{2.5}$ standard; (2) retaining PM_{10} as the indicator of a standard for thoracic coarse particles, retaining the level and form of the 24-hour PM_{10} standard, and revoking the PM_{10} annual standard; and (3) setting the secondary $PM_{2.5}$ standards identical to the primary standards. On February 24, 2009, the U.S. Court of Appeals for the District of Columbia Circuit issued its opinion in the case American Farm Bureau Federation v. U.S. EPA, 559 F. 3d 512 (D.C. Cir. 2009). The court remanded the primary annual $PM_{2.5}$ NAAQS to U.S. EPA because U.S. EPA failed to adequately explain why the standards provided the requisite protection from both short- and long-term exposures to fine particles, including protection for at-risk populations. American Farm Bureau Federation v. U.S. EPA, 559 F. 3d 512, 520–27 (D.C. Cir. 2009). With regard to the standards for PM_{10}, the court upheld U.S. EPA's decisions to retain the 24-hour PM_{10} standard to provide protection from thoracic coarse particle exposures and to revoke the annual PM_{10} standard. American Farm Bureau Federation, 559 F. 2d at 533–38. For the secondary $PM_{2.5}$ standards, the court remanded the standards to U.S. EPA because the Agency failed to adequately explain why setting the secondary PM standards identical to the primary standards provided the required

[16] Prior to the review initiated in 2007, the Staff Paper, rather than the PA, presented the EPA staff's considerations and conclusions regarding the adequacy of existing NAAQS and, when appropriate, the potential alternative standards that could be supported by the evidence and information.

[17] In the 2006 proposal, the EPA proposed to revise the 24-hour PM_{10} standard in part by establishing a new $PM_{10-2.5}$ indicator for thoracic coarse particles (i.e., particles generally between 2.5 and 10 μm in diameter). The EPA proposed to include any ambient mix of $PM_{10-2.5}$ that was dominated by resuspended dust from high density traffic on paved roads and by PM from industrial sources and construction sources. The EPA proposed to exclude any ambient mix of $PM_{10-2.5}$ that was dominated by rural windblown dust and soils and by PM generated from agricultural and mining sources. In the final decision, the existing PM_{10} standard was retained, in part due to an "inability…to effectively and precisely identify which ambient mixes are included in the [$PM_{10-2.5}$] indicator and which are not" (71 FR 61197, October 17, 2006).

protection for public welfare, including protection from visibility impairment. American Farm Bureau Federation, 559 F. 2d at 528–32. The U.S. EPA responded to the court's remands as part of the next review of the PM NAAQS, which was initiated in 2007 (discussed below).

In June 2007, the U.S. EPA initiated the fourth periodic review of the air quality criteria and the PM NAAQS by issuing a call for information in the Federal Register (72 FR 35462, June 28, 2007). Based on the NAAQS review process, as revised in 2008 and again in 2009,[18] the U.S. EPA held science/policy issue workshops on the primary and secondary PM NAAQS (72 FR 34003, June 20, 2007; 72 FR 34005, June 20, 2007), and prepared and released the planning and assessment documents that comprise the review process [i.e., IRP (U.S. EPA, 2008), ISA (U.S. EPA, 2009a)], REA planning documents for health and welfare (Office of Air and Radiation, 2009; U.S. EPA, 2009b), a quantitative health risk assessment (U.S. EPA, 2010b)[19] and an urban-focused visibility assessment (U.S. EPA, 2010a),[20] and PA (U.S. EPA, 2011)]. In June 2012, the U.S. EPA announced its proposed decision to revise the NAAQS for PM (77 FR 38890, June 29, 2012).

In December 2012, the U.S. EPA announced its final decisions to revise the primary NAAQS for PM to provide increased protection of public health (78 FR 3086, January 15, 2013). With regard to primary standards for $PM_{2.5}$, the U.S. EPA revised the level of the annual $PM_{2.5}$ standard[21] to 12.0 $\mu g/m^3$ and retained the 24-hour $PM_{2.5}$ standard, with its level of 35 $\mu g/m^3$. For the primary PM_{10} standard, the U.S. EPA retained the 24-hour standard, with its level of 150 $\mu g/m^3$, to continue to provide protection against effects associated with short-term exposure to thoracic coarse particles (i.e., $PM_{10-2.5}$). With regard to the secondary PM standards, the U.S. EPA generally retained the 24-hour and annual $PM_{2.5}$ standards[22] and the 24-hour PM_{10} standard to address visibility and non-visibility welfare effects. On judicial review, the revised standards were upheld in all respects. NAM v U.S. EPA, 750 F.3d 921 (D.C. Cir. 2014).

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[18] The history of the NAAQS review process, including revisions to the process, is discussed at http://www3.epa.gov/ttn/naaqs/review2.html.

[19] The quantitative assessment of health risks conducted in the last review was presented in the Quantitative Health Risk Assessment for Particulate Matter (U.S. EPA, 2010b). In the current review, quantitative assessments for health-related exposures and risks, if warranted, would be presented in the Health Risk and Exposure Assessment (HREA). For consistency with the documents developed under the current NAAQS process, the Quantitative Health Risk Assessment for Particulate Matter (U.S. EPA, 2010b) from the last review will be referenced in this document as the 2010 HREA.

[20] The quantitative assessment of welfare effects conducted in the last review was presented, in part, in the Urban-Focused Visibility Assessment (U.S. EPA, 2010a). In the current review, quantitative assessments for welfare effects, if warranted, would be presented in the Welfare Risk and Exposure Assessment (WREA). The Urban-Focused Visibility Assessment (U.S. EPA, 2010a) from the last review will be referenced in this document as the 2010 UFVA.

[21] The U.S. EPA also eliminated the option for spatial averaging.

[22] Consistent with the primary standard, the U.S. EPA eliminated the option for spatial averaging with the annual standard.

P.2 Purpose and Overview of the Integrated Science Assessment

The Integrated Science Assessment (ISA) is a comprehensive evaluation and synthesis of the policy-relevant science "useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in ambient air," as described in Section 108 of the Clean Air Act (CAA, 1990a). This ISA communicates critical science judgments of the health and welfare criteria for particulate matter (PM). As such, this ISA serves as the scientific foundation for the review of the current primary (health-based) and secondary (welfare-based) National Ambient Air Quality Standards (NAAQS) for PM. In terms of the evaluation of the welfare-based evidence, the PM ISA focuses specifically on the nonecological effects of PM (i.e., visibility, materials effects, and climate) because the ecological effects are assessed in the ISA for Oxides of Nitrogen, Oxides of Sulfur, and Particulate Matter—Ecological Criteria as a result of these criteria pollutants being interrelated through complex chemical and physical atmospheric processes and all contributing to nitrogen (N) and sulfur (S) deposition (U.S. EPA, 2016). While the focus of the evaluation of the visibility and climate evidence is on PM, for materials effects, as detailed in the Integrated Review Plan (IRP), the PM ISA summarizes soiling and deterioration of materials attributable to PM and related N and S components because of the difficulty associated with isolating the effects of gaseous and particulate N and S wet deposition and because the ISA for Oxides of Nitrogen, Oxides of Sulfur, and Particulate Matter—Ecological Criteria focuses only on ecological effects (U.S. EPA, 2016).

This ISA evaluates relevant scientific literature published since the 2009 PM ISA [(U.S. EPA, 2009a) or 2009 PM ISA], integrating key information and judgments contained in the 2009 PM ISA and previous assessments of PM, i.e., 2004 AQCD for PM (U.S. EPA, 2004), 1996 AQCD for PM (U.S. EPA, 1996), 1982 AQCD for PM and Sulfur Oxides (U.S. EPA, 1982) and its Addendum (U.S. EPA, 1986), and the 1969 AQCD for PM (NAPCA, 1969). Thus, this ISA updates the state of the science that was available for the 2009 PM ISA, which informed decisions on the primary and secondary PM NAAQS in the review completed in 2012. In 2012, the U.S. EPA lowered the annual $PM_{2.5}$ standard to a mean of 12 $\mu g/m^3$, which is based on the annual mean averaged over 3 years, while retaining the 24-hour $PM_{2.5}$ standard of 35 $\mu g/m^3$, which is based on the 98th percentile averaged over 3 years (78 FR 3086). As part of the primary annual $PM_{2.5}$ standard, the U.S. EPA eliminated the spatial averaging provision to avoid disproportionate impacts on susceptible populations (i.e., populations potentially at increased risk of a PM-related health effect). The $PM_{2.5}$ standards are meant to provide increased protection for children, older adults, and people with pre-existing heart and lung disease as well as other potential susceptible populations against an array of $PM_{2.5}$-related health effects including premature mortality, increased hospital admissions and emergency department (ED) visits, and the development of chronic respiratory disease. Additionally, the U.S. EPA retained the current primary 24-hour PM_{10} standard at a level of 150 $\mu g/m^3$, which is not to be exceeded more than once per year over 3 years, to protect against health effects due to short-term exposure to thoracic coarse particles ($PM_{10-2.5}$) including premature mortality and increased hospital admissions and ED visits (78 FR 3086).

In terms of the secondary PM standards, the U.S. EPA retained the annual $PM_{2.5}$ standard at 15 $\mu g/m^3$ as well as the 24-hour $PM_{2.5}$ standard of 35 $\mu g/m^3$ and the 24-hour PM_{10} standard of 150 $\mu g/m^3$ (78 FR 3086). However, the form of the annual secondary $PM_{2.5}$ standard was changed to remove the option of spatial averaging. These secondary standards protect against non-visibility welfare effects including ecological effects, effects on materials, and climate impacts. To protect against PM-related visibility impairment, the U.S. EPA identified a target degree of protection defined as a $PM_{2.5}$ visibility index of 30 deciviews (dv), which is based on the 90th percentile of 24-hour average $PM_{2.5}$ concentrations over 3 years (78 FR 3086). However, an U.S. EPA analysis determined that the current secondary 24-hour $PM_{2.5}$ standard would provide sufficient protection, and in some cases greater protection, therefore a distinct secondary standard was not needed to provide requisite protection for both visibility and non-visibility related welfare effects.

This new review of the primary and secondary PM NAAQS is guided by several policy-relevant questions that are identified in The Integrated Review Plan for the National Ambient Air Quality Standards for Particulate Matter (U.S. EPA, 2016). To address these questions and update the scientific judgments in the 2009 PM ISA (U.S. EPA, 2009a), this ISA aims to:

- Assess whether new information (since the last PM NAAQS review) further informs the relationship between exposure to PM and specific health and nonecological welfare effects?
- Inform whether the current indicators (i.e., $PM_{2.5}$ for fine particles and PM_{10} for thoracic coarse particles), averaging times (e.g., 24-hour average, annual average), and levels of the PM NAAQS are appropriate?

In addressing policy-relevant questions, this ISA aims to characterize the independent health and welfare effects of PM, specifically $PM_{2.5}$ (fine PM; particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 m) and $PM_{10-2.5}$ (thoracic coarse or coarse PM; particulate matter with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm) and whether there is evidence of an independent health effect for other size fractions [e.g., ultrafine particles (UFP), generally considered as particulates with a diameter less than or equal to 0.1 μm (typically based on physical size, thermal diffusivity or electrical mobility) (U.S. EPA, 2009a)] or specific PM components (e.g., metals). In the characterization of whether there is evidence of an independent health and welfare effect due to PM, the ISA considers possible influences of other atmospheric pollutants, including both gaseous (i.e., O_3, NO_2, SO_2, and CO) and other PM size fractions. The information summarized in this ISA will serve as the scientific foundation for the review of the current primary and secondary PM NAAQS.

P.3 Process for Developing Integrated Science Assessments

The U.S. EPA uses a structured and transparent process for evaluating scientific information and determining the causal nature of relationships between air pollution exposures and health effects [details provided in the Preamble to the Integrated Science Assessments (U.S. EPA, 2015)]. The ISA

development process describes approaches for literature searches, criteria for selecting and evaluating relevant studies, and a framework for evaluating the weight of evidence and forming causality determinations. Table P-2 provides a description of each of the five causality determinations and the types of scientific evidence that is considered for each category for both health and welfare effects.

Table P-2. Weight of evidence for causality determinations.

	Health Effects	Ecological and Other Welfare Effects
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (e.g., doses or exposures generally within one to two orders of magnitude of recent concentrations). That is, the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent effects, or (2) observational studies that cannot be explained by plausible alternatives or that are supported by other lines of evidence (e.g., animal studies or mode of action information). Generally, the determination is based on multiple high-quality studies conducted by multiple research groups.	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. Controlled exposure studies (laboratory or small- to medium-scale field studies) provide the strongest evidence for causality, but the scope of inference may be limited. Generally, the determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many lines of evidence that reinforce each other.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. For example: (1) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent, or (2) animal toxicological evidence from multiple studies from different laboratories demonstrate effects, but limited or no human data are available. Generally, the determination is based on multiple high-quality studies.	Evidence is sufficient to conclude that there is a likely causal association with relevant pollutant exposures. That is, an association has been observed between the pollutant and the outcome in studies in which chance, confounding, and other biases are minimized but uncertainties remain. For example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, the determination is based on multiple studies by multiple research groups.

Table P-2. (Continued): Weight of evidence for causality determinations.

	Health Effects	Ecological and Other Welfare Effects
Suggestive of, but not sufficient to infer, a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures but is limited, and chance, confounding, and other biases cannot be ruled out. For example: (1) when the body of evidence is relatively small, at least one high-quality epidemiologic study shows an association with a given health outcome and/or at least one high-quality toxicological study shows effects relevant to humans in animal species, or (2) when the body of evidence is relatively large, evidence from studies of varying quality is generally supportive but not entirely consistent, and there may be coherence across lines of evidence (e.g., animal studies or mode of action information) to support the determination.	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but chance, confounding, and other biases cannot be ruled out. For example, at least one high-quality study shows an effect, but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations and lifestages, are mutually consistent in not showing an effect at any level of exposure.	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies examining relationships with relevant exposures are consistent in failing to show an effect at any level of exposure.

Source: U.S. EPA (2015).

As part of this process, the ISA is reviewed by the Clean Air Scientific Advisory Committee (CASAC), which is a formal independent panel of scientific experts, and by the public. As this ISA informs the review of the primary and secondary PM NAAQS, it integrates and synthesizes information characterizing exposure to PM and potential relationships with health and welfare effects. Relevant studies include those examining atmospheric chemistry, spatial and temporal trends, and exposure assessment, as well as U.S. EPA analyses of air quality and emissions data. Relevant health research includes epidemiologic, controlled human exposure, and toxicological studies on health effects, as well as studies on dosimetry and biological plausibility. Additionally, relevant welfare research includes studies examining visibility impairment, effects on materials, and climate impacts.

The U.S. EPA initiated the current review of the primary and secondary PM NAAQS in December 2014 with a call for information from the public (U.S. EPA, 2013). Subject-area experts and the public were also able to recommend studies and reports to consider for the ISA during a science/policy issue "kick-off" workshop held at the U.S. EPA in February 2015. Thereafter, the U.S. EPA routinely conducted literature searches to identify relevant peer-reviewed studies published since the previous ISA (i.e., since May 2009). Multiple search methods were used [Preamble to the ISAs (U.S. EPA, 2015), Section 2], including searches in the PubMed and Web of Science databases. These

searches were meant to broadly capture all potentially relevant PM literature. To ensure the most policy-relevant evaluation of the current state of the science the scope of this PM ISA reflects not only the evolving PM literature base, but also the ability of the studies evaluated to directly inform the policy-relevant questions that form the basis of this review. Using both the scope of this ISA, detailed below, as well as the policy-relevant questions outlined in the PM IRP, studies that were uninformative based on title screening were excluded. Studies that were judged to be potentially relevant based on review of the abstract or full text and "considered" for inclusion in the ISA are documented in the Health and Environmental Research Online (HERO) website. The HERO project page for this ISA (https://hero.epa.gov/hero/particulate-matter) contains the references that are cited in the ISA, the references that were considered for inclusion but not cited, and electronic links to bibliographic information and abstracts.

P.3.1. Scope of the ISA

As initially detailed in the PM IRP (U.S. EPA, 2016) and further expanded upon here, when evaluating the broad body of literature across scientific disciplines, the U.S. EPA considers whether the studies fall within the scope of the PM ISA (i.e., provide information which can address key policy-relevant questions). As a result, the focus of the PM ISA with respect to the health effects evidence is on studies of short-term (i.e., hours up to 1 month) and long-term (i.e., 1 month to years) exposures conducted at concentrations of PM that are relevant to the range of human exposures across ambient microenvironments (up to 2 mg/m^3, which is one to two orders of magnitude above ambient concentrations), and (1) include a composite measure of PM[23] or (2) characterize PM and apply some approach to assess the direct effect of PM when the exposure of interest is a source-based mixture (e.g., diesel exhaust, gasoline exhaust, wood smoke). For epidemiologic studies, the scope is further refined when evaluating the evidence for those health outcomes where the 2009 PM ISA concluded that a "causal relationship exists" (i.e., short- and long-term $PM_{2.5}$ exposure and mortality and cardiovascular effects) to ensure the evaluation of the evidence focuses on the studies that are the most policy-relevant. As such, the focus is on those studies conducted in areas where mean $PM_{2.5}$ concentrations are <20 $\mu g/m^3$ or in the case of a multicity study where more than half of the cities have concentrations <20 $\mu g/m^3$. However, studies where mean $PM_{2.5}$ concentrations exceed 20 $\mu g/m^3$ are included if the studies address specific areas where the evidence was limited, as identified in the 2009 PM ISA, such as copollutant confounding. The scope is broader for experimental studies when examining biological plausibility for PM health effects, and in some cases, includes in vitro studies, studies that use intratracheal (IT) installation, studies examining relative toxicity, and studies conducted at concentrations >2 mg/m^3.

In the first case, studies that focus on a single component, group of components, or source, must also examine a composite measure of PM (e.g., mass of $PM_{2.5}$ and/or $PM_{10-2.5}$, or in the case of ultrafine particles [UFP] mass, particle number, etc.). This requirement facilitates a comparison of effects or

[23] Composite measures of PM may include mass, volume, surface area, or number concentration.

associations observed for individual components or alternative metrics to the current mass-based PM indicators. For experimental studies, to assess the relationship between $PM_{2.5}$ components and specific health effects this ISA relies on the approach initially outlined in the 2009 PM ISA and further refined in Stanek et al. (2011). This approach is consistent with the Health Effects Institute (HEI) Review Panel of the National Particle Component Toxicity (NPACT) initiative that states both source categories and component concentrations should be used directly in the health analyses with a focus on examining consistencies and differences between the two approaches (Lippmann et al., 2013). As a result, experimental studies included within this ISA fulfill the following four criteria (1) exposures examined consist of $PM_{2.5}$ from U.S. airsheds or those representative of the U.S. (e.g., Europe, Canada); (2) examined at least five PM components; (3) grouped PM components using statistical methods, for which the groups were not predefined based on common physical or chemical properties (e.g., water soluble vs. nonsoluble); and (4) applied a formal statistical analysis to investigate the relationship between groups of PM components or PM sources and health effects. The criteria applied to both experimental and epidemiologic studies in the evaluation of PM components ensures that a systematic approach is used in both identifying and evaluating those studies that examine PM components.

The second case primarily applies to experimental studies that attempt to disentangle the effect of PM on health from a complex air pollution mixture of particles, gases, and components distributed between the gas and particle phases. Studies that conduct an assessment of the PM effect from a source-based mixture (e.g., wood smoke, diesel exhaust, gasoline exhaust, etc.) are only included if they use filtration (e.g., a particle trap) or another approach to differentiate between effects due to the mixture and effects due to the particles alone.

Whereas the preceding paragraphs focused broadly on the scope of the entire PM ISA, there are additional nuances that further frame the scope of the ISA, specifically with respect to UFPs. UFPs have often been defined as particles <0.1 μm (U.S. EPA, 2009a), but depending on the scientific discipline, the methods employed and particle sizes examined to assess the UFP-health effects relationship varies. UFP exposures in animal toxicological and controlled human exposure studies typically use a particle concentrator, which can result in exposures to particles <0.30 μm (Section 2.4.3.1). While toxicological studies typically rely on examining UFP mass, epidemiologic studies examine multiple UFP metrics including particle number concentration (NC), mass concentration (MC), and surface area concentration (SC). However, depending on the monitor used and the metric, the UFP size distribution that could be included within each of these ranges can vary. Some studies that examine NC use no additional size classification, instead measuring NC over the entire size range of the particle counter. In instances where the entire size range is measured, limited available measurement data in the U.S. and Europe indicates that approximately 67 to 90% of NC represents particles <0.1 μm (Section 2.4.3.1). Studies that examine MC or SC often include a range of particle sizes up to 0.3 μm. Currently, a consensus has not been reached within the scientific community on the metric that best represents exposure to UFPs (Baldauf et al., 2016). As a result, in this ISA the focus of the evaluation of the UFP-health effects relationship is on particles <0.3 μm for MC and SC metrics included in experimental studies, and any size range that

includes particles <0.1 μm for NC. Focusing on these criteria when evaluating UFP studies will provide the most comprehensive assessment of UFPs and ensure that the metric examined represents primarily the UFP size range.

Across disciplines, studies defined as examining UFPs, but focusing on the sources, transport, and fate of fibers and unique nano-objects (namely, dots, hollow spheres, plates, rods, fibers, tubes) are not reviewed because substantial exposures to fibers and unique nano-objects generally occur in the occupational settings rather than the ambient environment. Furthermore, the in vivo disposition of unique nano-objects is not likely relevant to the behavior of ultrafine (UF) aerosols found in ambient air, which are created by combustion sources and photochemical formation of secondary organic aerosols. However, some studies focusing on engineered nano- or ultrafine particles (e.g., carbon black, titanium dioxide) are included where they contribute to an understanding of the dosimetry or biological plausibility of PM.

In addition to the specific parameters that broadly form the overall scope of the review of PM and health effects, additional criteria were applied for the evaluation of the evidence for cancer. As detailed in the PM IRP, the PM ISA focuses on whether PM can directly cause cancer through only inhalation exposures at ambient and near-ambient concentrations (i.e., up to 2 mg/m^3). When evaluating the epidemiologic evidence for cancer, consistent with the overall scope of the ISA, the focus is on those studies with composite measures of PM. Whereas the ISA tends not to focus the evaluation of the health effects evidence on in vitro studies, for the purposes of examining the mutagenicity of PM in vitro systems are discussed because they inform the biological pathways underlying cancer. While some components of PM are known carcinogens (e.g., benzene), as previously stated the focus of this ISA is on composite measures of PM (e.g., $PM_{2.5}$) and, where applicable, comparison to effects or associations observed for individual PM components to help inform the adequacy of current mass-based PM indicators. As such, the relationship between PM exposure and cancer is evaluated similarly to that of other health effects, resulting in the exclusion of studies that examine individual PM components without a composite PM measure. The evaluation of cancer includes studies that use PM filter extracts with the understanding that bioavailability of PM components in vivo is a complex issue not easily mimicked by extraction of PM collected on filters. Overall, the evaluation of cancer in the ISA will primarily focus on studies of inhaled PM since these studies are more relevant to ambient exposure conditions with the recognition of the extensive historical evaluations on the mutagenicity, genotoxicity, and carcinogenicity of whole PM exposures (i.e., not defined by size fraction).

For nonecological welfare effects (i.e., visibility, climate, and materials effects), this ISA will build on information available during the last review describing the role of PM in visibility impairment, radiative forcing resulting in global and regional climate change, and materials damage and soiling. For visibility effects, studies are included which advance our understanding of visual impairment of airborne PM, including studies of atmospheric chemistry, visibility preference, or other measures of adversity to public welfare, in urban and rural settings. For climate effects, this ISA focuses on climate as the welfare effect as listed in the Clean Air Act Amendments of 1970 with a focus on radiative forcing, surface

meteorological trends, and climate feedbacks, and not on downstream ecosystem effects, human health effects, or future air quality projections resulting from changes in climate (CAAA, 1970). The primary literature base for the evaluation of the effects of airborne and deposited PM on climate comes from recent national and international climate assessments such as the National Climate Assessment (Melillo et al., 2014) and International Panel on Climate Change (IPCC, 2014), as well as other recent and more focused reports relevant to PM climate forcing [e.g., (U.S. EPA, 2012)]. The focus is on studies that inform the independent role of PM in climate forcing as well as effects on U.S. national and regional climate. For effects on materials, studies included in the PM ISA examine the role of PM and relevant precursor gases on materials damage and soiling. Specifically, studies that examine both particulate and gaseous contributions from oxides of nitrogen and oxides of sulfur along with other PM components are included here due to the difficulty associated with isolating the effects of gaseous and particulate N and S wet deposition.

P.3.2. Evaluation of the Evidence

The Preamble to the ISAs (U.S. EPA, 2015) describes the general framework for evaluating scientific information, including criteria for assessing study quality and developing scientific conclusions. Aspects specific to evaluating studies of PM are described in the Annex to the Preface, which were applied to studies that fit the overall scope of the PM ISA. Categories of health and welfare effects were considered for evaluation in this ISA if they were examined in previous U.S. EPA assessments for PM or in multiple recent studies. Therefore, in this ISA the broad health effects categories evaluated include those considered in the 2009 PM ISA (i.e., respiratory effects, cardiovascular effects, central nervous system effects, cancer, and mortality) along with the addition of metabolic effects, while new research indicates it is more appropriate to further refine the category of reproductive and developmental effects to instead focus overall conclusions specifically on fertility and pregnancy effects, and birth outcomes separately. While the welfare effects categories evaluated include visibility impairment, effects on materials, and climate.

In forming the key science judgments for each of the health and welfare effects categories evaluated, the PM ISA draws conclusions about relationships between PM exposure and health effects by integrating information across scientific disciplines and related health outcomes and synthesizing evidence from previous and recent studies. To impart consistency in the evaluation of health effects evidence for epidemiologic studies, additional parameters to those outlined in the scope (Section P.3.1) were developed. To facilitate a comparison of results across epidemiologic studies, risk estimates were standardized to a defined increment for both short- and long-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$, unless otherwise noted in the text. To determine the appropriate increment the distribution of $PM_{2.5}$ and $PM_{10-2.5}$ concentrations were examined across the three most recent years of air quality data (2012–2014) within the U.S. For both $PM_{2.5}$ and $PM_{10-2.5}$, an increment of 10 $\mu g/m^3$ was defined for short-term exposure studies which approximates the 50th–95th percentile of concentrations and accounts for the variability observed in daily $PM_{2.5}$ concentrations. An increment of 5 $\mu g/m^3$ was defined for long-term exposure

studies which approximates the 25th−75th percentile of concentrations and represents the variation observed in long-term mean concentrations. Due to the lack of an extensive monitoring network for UFPs within the U.S., results from studies examining UFP are not standardized and reflect the increment of exposure defined in each study evaluated. Additionally, in the assessment of correlations, either with other copollutants or variables, in epidemiologic studies high, moderate, or low correlations are explicitly defined as the following: low correlation, $r < 0.40$; moderate correlation, $r \geq 0.40$ and $r < 0.70$; and high correlation, $r \geq 0.70$. Consistency in the interpretation of the epidemiologic evidence through approaches such as the standardization of risk estimates and the evaluation of correlations, in combination with the integration of evidence across scientific disciplines supports a thorough evaluation of the current state of the science for PM.

In the evaluation of the evidence determinations are made about causation, not just association, and are based on judgments of aspects such as the consistency of evidence within a discipline, coherence of effects across disciplines, and biological plausibility of observed effects as well as related uncertainties. The ISA uses a formal causal framework [Table II of the Preamble to the ISAs (U.S. EPA, 2015)] to classify the weight of evidence according to the five-level hierarchy summarized below.

- Causal relationship: the pollutant has been shown to result in health and welfare effects at relevant exposures based on studies encompassing multiple lines of evidence and chance, confounding, and other biases can be ruled out with reasonable confidence.
- Likely to be a causal relationship: there are studies in which results are not explained by chance, confounding, or other biases, but uncertainties remain in the health and welfare effects evidence overall. For example, the influence of co-occurring pollutants is difficult to address, or evidence across scientific disciplines may be limited or inconsistent.
- Suggestive of, but not sufficient to infer, a causal relationship: health and welfare effects evidence is generally supportive but not entirely consistent or is limited overall. Chance, confounding, and other biases cannot be ruled out.
- Inadequate to infer the presence or absence of a causal relationship: there is insufficient quantity, quality, consistency, or statistical power of results from studies of health and welfare effects.
- Not likely to be a causal relationship: several adequate health and welfare effects studies, examining the full range of anticipated exposure concentrations and for health effects, potential at-risk populations and lifestages consistently show no effect.

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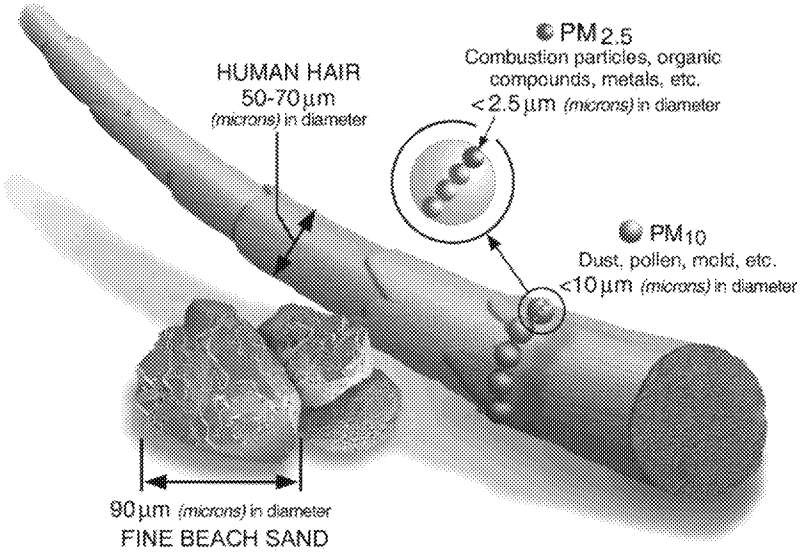
EXECUTIVE SUMMARY

Purpose and Scope of the Integrated Science Assessment

This Integrated Science Assessment (ISA) is a comprehensive evaluation and synthesis of policy-relevant science aimed at characterizing exposures to ambient particulate matter (PM), and health and welfare effects associated with these exposures.[24] PM is a mixture of solid particles and liquid droplets found in the ambient air[25], which encompasses multiple size fractions (e.g., fine PM [$PM_{2.5}$, particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm]; thoracic coarse or coarse PM [$PM_{10-2.5}$, particulate matter with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm]; and ultrafine particles [UFPs, generally considered as particulates with a diameter less than or equal to 0.1 μm, typically based on physical size, thermal diffusivity or electrical mobility]) and is comprised of various components (e.g., metals, black carbon, etc.) (Figure ES-1). The evaluation of the science and the overarching conclusions of the ISA serves as the scientific foundation for the review of the primary (health-based) and secondary (welfare-based) National Ambient Air Quality Standard (NAAQS) for PM. This ISA focuses on nonecological welfare effects[26] because ecological effects resulting from deposition of PM and PM components are being considered in a separate assessment as part of the review of the secondary (welfare-based) NAAQS for oxides of nitrogen and sulfur, and PM (U.S. EPA, 2018).

[24] The general process for developing an ISA, including the framework for evaluating weight of evidence and drawing scientific conclusions and causal judgments, is described in a companion document, *Preamble to the Integrated Science Assessments* (U.S. EPA, 2015), www.epa.gov/isa.
[25] As defined by U.S. EPA, https://www.epa.gov/pm-pollution/particulate-matter-pm-basics.
[26] From this point forward referred to as welfare effects.



Source: Permission pending, U.S. EPA[27]

Figure ES-1 Comparison of PM size fractions.

In 2012, the U.S. Environmental Protection Agency (U.S. EPA) established a new annual $PM_{2.5}$ primary standard of 12 $\mu g/m^3$ (the annual mean averaged over 3 years) and retained the 24-hour $PM_{2.5}$ standard of 35 $\mu g/m^3$ (the 98th percentile averaged over 3 years) (75 FR 3086).[28] For the primary PM_{10} standard, the U.S. EPA retained the 24-hour standard of 150 $\mu g/m^3$ (not to be exceeded more than once per year on average over 3 years) to continue to provide protection against effects associated with short-term exposure to thoracic coarse particles (i.e., $PM_{10-2.5}$). Regarding the secondary PM standards, the U.S. EPA retained the 24-hour (i.e., 35 $\mu g/m^3$) and annual (i.e., 15 $\mu g/m^3$) $PM_{2.5}$ standards[29] and the 24-hour PM_{10} standard (i.e., 150 $\mu g/m^3$) to address visibility and nonvisibility welfare effects. On judicial review, the revised and retained standards were upheld in all respects. NAM v EPA, 750 F.3d 921 (D.C. Cir. 2014).

This ISA updates the 2009 ISA for Particulate Matter [(U.S. EPA, 2009) hereafter referred to as the 2009 PM ISA] with studies and reports published from January 2009 through approximately January 2018. The U.S. EPA conducted in-depth searches to identify peer-reviewed literature on relevant topics such as health and welfare effects, atmospheric chemistry, ambient concentrations, and exposure. Information was also solicited from subject-matter experts and the public during a kick-off workshop held

[27] https://www.epa.gov/pm-pollution/particulate-matter-pm-basics.
[28] The legislative requirements and history of the PM NAAQS are described in detail in the Preface to this ISA.
[29] Consistent with the primary standard, the U.S. EPA eliminated the option for spatial averaging with the annual standard.

at the U.S. EPA in February 2015. To fully describe the state of available science, the U.S. EPA also included in this ISA the most relevant studies from previous assessments.

As in the 2009 PM ISA, this ISA determines the causal nature of relationships between health effects and exposure to $PM_{2.5}$, $PM_{10-2.5}$, and UFPs (CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11). To address this task a defined scope was developed to focus on those studies that inform whether PM exposure directly causes health effects (see Preface). Health effects are considered in relation to exposures at concentrations of PM that are relevant to the range of human exposures across ambient microenvironments, specifically within one to two orders of magnitude of current conditions (i.e., up to 2 mg/m^3) (Preface, Section P.3.1). The ISA also evaluates the relationship between PM components and sources to assess whether there is evidence that a component, group of components, or source is more closely related to health effects than PM mass (see Preface). Additionally, the ISA evaluates whether specific populations or lifestages are at increased risk of PM-related health effects. The ISA also determines the causal nature of relationships between PM and welfare effects. In the evaluation of the welfare-based evidence (CHAPTER 13), the PM ISA focuses specifically on the nonecological welfare effects of PM (i.e., visibility, materials effects, and climate) because the ecological effects are assessed in the ISA for Oxides of Nitrogen, Oxides of Sulfur and Particulate Matter – Ecological Criteria as a result of these criteria pollutants being inter-related through complex chemical and physical atmospheric processes and all contributing to nitrogen (N) and sulfur (S) deposition (U.S. EPA, 2018). However, in the assessment of effects on materials the PM ISA summarizes soiling and deterioration of materials attributable to PM and related nitrogen (N) and sulfur (S) components because of the difficulty associated with isolating the effects of gaseous and particulate N and S wet deposition and because the ISA for Oxides of Nitrogen, Oxides of Sulfur and Particulate Matter – Ecological Criteria focuses only on ecological effects (U.S. EPA, 2018).

Key to interpreting the health and welfare effects evidence is understanding the sources, chemistry, and distribution of PM in the ambient air (CHAPTER 2). It is these atmospheric relationships and processes that influence human exposure (CHAPTER 3) and the uptake of inhaled PM in the respiratory tract (CHAPTER 4). The uptake of PM and its deposition in the body directly influences the biological mechanisms by which PM could potentially result in a health effect (CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11). Further, the ISA aims to characterize the independent effect of PM (i.e., $PM_{2.5}$, $PM_{10-2.5}$, and UFP) on health (CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11). The ISA also informs policy-relevant issues (Section 1.6 and CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, CHAPTER 11, and CHAPTER 12), such as (1) potential copollutant confounding (Section 1.5.1); (2) timing of effects (i.e., averaging time of exposure metric and lag at which associations are observed in epidemiologic studies (Section 1.5.2); (3) PM concentration-response relationship(s), and evaluation of potential thresholds for effects (Section 1.5.3); (4) PM components and sources and relationships with health effects (Section 1.5.4); and (5) populations or lifestages at increased risk for health effects related to PM exposure (Section 1.5.5).

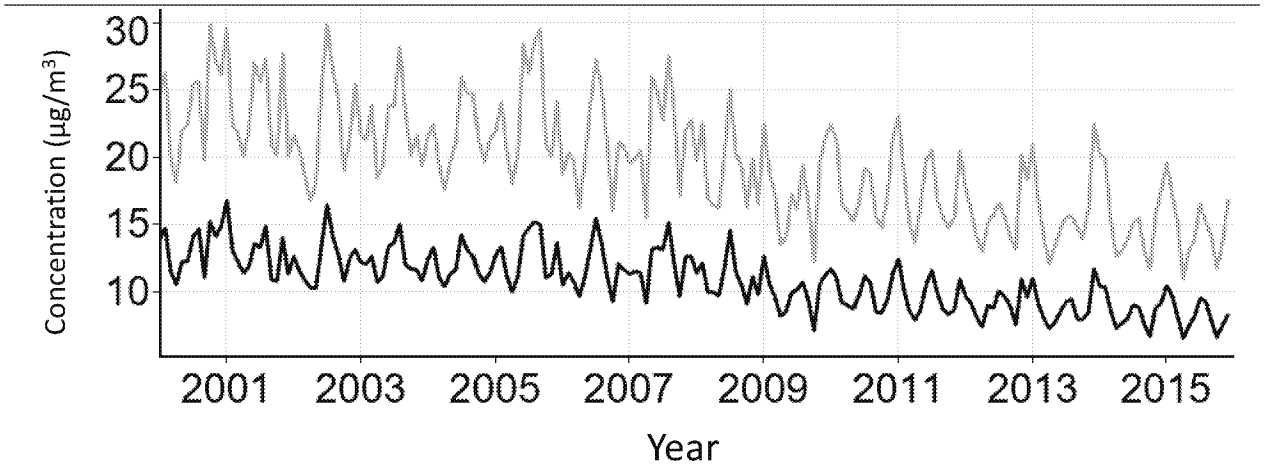
Sources and Exposure to PM

The main objective of the ISA is to characterize health and welfare effects related to ambient PM exposure. This requires understanding PM sources, atmospheric formation, measurement methods, and concentrations. Additionally, with respect to characterizing the health effects of PM it requires understanding the factors that affect both exposure to ambient PM and the uncertainty in estimating exposure. These factors include unmeasured variability in $PM_{2.5}$, $PM_{10-2.5}$, and UFP concentrations and size distributions, exposure to copollutants, and uncharacterized PM composition.

Particulate matter is comprised of components that are directly emitted (primary PM) as well as formed through atmospheric chemical reactions involving gaseous precursors (secondary PM) (Section 2.3). Both primary and secondary PM contribute substantially to overall PM mass in ambient air. Within an urban environment most primary $PM_{2.5}$ emissions are from anthropogenic sources, and include some combination of industrial activities, motor vehicles, cooking, and fuel combustion. However, in many locations secondary PM formed from the precursors sulfur dioxide (SO_2), oxides of nitrogen (NO_X), ammonia (NH_3), and volatile organic compounds (VOCs), accounts for the majority of $PM_{2.5}$ mass. Direct emissions of primary $PM_{2.5}$ have decreased slightly (~9% since 2002) over the past decade, along with a substantial decrease in emissions since 2006 of the major $PM_{2.5}$ precursors SO_2 and NO_X, 65% and 30%, respectively. $PM_{10-2.5}$ is almost entirely primary in origin, composed largely of crustal material, sea salt, and biological material. National average $PM_{10-2.5}$ concentrations have changed little over the past decade. Ambient UFPs originate from two distinct processes, primary particles directly emitted from specific sources like motor vehicles and new particle formation by photochemical processes under favorable atmospheric conditions.

There are well-established federal reference methods (FRM) and national monitoring networks for $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ (Section 2.4). Recent monitoring initiatives include the implementation of the National Core multipollutant monitoring network, which includes $PM_{2.5}$ and $PM_{10-2.5}$ measurements along with a suite of other pollutants, a new near road monitoring network that includes $PM_{2.5}$ monitors at 36 sites, and the first routine monitoring of particle number count at 23 sites. Satellite-based measurements in conjunction with chemical transport models have also become increasingly used for estimating $PM_{2.5}$ concentrations. In general, the fraction of PM_{10} accounted for by $PM_{2.5}$ is higher in the eastern U.S. than in the western U.S. Compared to $PM_{2.5}$, $PM_{10-2.5}$ concentrations are more spatially variable. The limited amount of available UFP measurements data indicated that the highest UFP concentrations occur in the winter and near roads with heavy traffic, often over short time periods. Overall, UFP concentrations are more spatially variable than $PM_{2.5}$. As Figure 2-22 shows, national average $PM_{2.5}$ concentrations decreased by about 5 $\mu g/m^3$ from 2000 to 2015. Much of this decrease is accounted for by a corresponding decrease in sulfate concentrations, especially in the eastern U.S., attributed to reduced SO_2 emissions. Sulfate concentrations are mainly associated with $PM_{2.5}$ and have historically been highest in summer. The reduction in $PM_{2.5}$ and sulfate concentrations has coincided with shifts from summer, as the season with the highest national average concentration, to a more even

distribution of $PM_{2.5}$ concentrations between summer and winter, and to an increase in the contribution of $PM_{10-2.5}$ to PM_{10} concentrations.



Black = mean, gray = 90th percentile.
Source: Permission pending, Chan et al. (2018).

Figure ES-2 Long-term trend in national monthly and annual average $PM_{2.5}$ concentrations (µg/m³) from 2000–2015.

Fixed-site monitoring is frequently used for obtaining $PM_{2.5}$ exposure surrogates in both short-term and long-term exposure epidemiologic studies (Section 3.3), given that spatial variability in $PM_{2.5}$ concentration tends to be lower than for other size fractions. Fixed-site monitoring for $PM_{10-2.5}$ has been performed by different methods. It is important to consider the method used in order to characterize errors and uncertainties in the data that are related both to the monitoring method and the proximity of the individual receptor to the monitor because $PM_{10-2.5}$ is typically more spatially variable than $PM_{2.5}$. Condensation particle counter (CPC) is most commonly used to measure UFP. However, some portion of the UFP size distribution may be omitted using CPC, since they do not typically measure particles smaller than 10 nm. UFP also tends to be more spatially variable than $PM_{2.5}$, contributing to uncertainties in exposure assignments.

Modeling approaches, such as spatial interpolation methods, land use regression, dispersion models, and chemical transport models (CTMs), have for years provided estimates of exposure concentration where no measurements are available. More recently, hybrid models drawing input from CTMs, satellite observations of aerosol optical density, surface measurements of PM concentration, and land use variables have become available. Most studies using hybrid methods are applied to model $PM_{2.5}$ and have out-of-sample cross-validations with $R^2 > 0.8$. Models are employed less frequently to estimate

$PM_{10-2.5}$ and UFP exposure concentration, despite $PM_{10-2.5}$ and UFP typically being more spatially variable than $PM_{2.5}$. This is related in part to less availability of input data.

When particles enter a building envelope, they may be lost during the process of infiltration to indoor, to produce an infiltration factor (F_{inf}) < 1 (Section 3.4). F_{inf} varies with season, window opening, building age, wind speed and particle size distribution (with F_{inf} lower for $PM_{10-2.5}$ and UFP compared with $PM_{2.5}$). When examining the influence of estimated exposure concentrations on health effect estimates in a time-series study of short-term PM exposure, use of a fixed-site monitor in lieu of a microenvironmental model that accounted for infiltration produced considerably attenuated health effect estimates, which resulted in an underestimation of the health effect. Infiltration of PM through a building envelope may change the temporal variability of the indoor PM concentration time-series, resulting in reduced correlation between the health effect of interest and the estimated exposure concentration. In the examination of how exposure concentration estimates influence health effect estimates in an epidemiologic study of long-term PM exposure, simulating indoor concentrations produced unbiased health effect estimates.

In summary, exposure error tends to produce underestimation of health effects in epidemiologic studies of PM exposure, although bias in either direction can occur. Recent improvements in estimating spatial resolution of the $PM_{2.5}$ concentration surface have reduced bias and uncertainty in health effects estimates. $PM_{10-2.5}$ and UFP concentrations tend to be more spatially variable than $PM_{2.5}$ concentrations, but data are either unavailable or less often available to fit or validate hybrid models for those size fractions. As a result, there is typically less uncertainty in health effect estimates derived from both monitored and modeled exposure estimates for $PM_{2.5}$ compared with either $PM_{10-2.5}$ or UFP.

Dosimetry of Inhaled PM

Particle dosimetry characterizes the intake, deposition, and retention of PM in the respiratory tract (CHAPTER 4). The basic understanding of particle dosimetry has not changed since the last review. Quantification of the fraction of inhaled particles reaching the lung and the small fraction of deposited particles that enter the blood, distribute around the body, and accumulate in organs and tissues has improved. Understanding the dosimetry of particles is crucial to providing evidence that supports whether it is biologically plausible that PM exposure can lead to a range of health effects spanning multiple organ systems.

A variety of factors influence the amount of inhaled particles deposited and retained in the respiratory tract and include exposure concentration and duration, activity and breathing conditions (e.g., nasal vs. oronasal route and minute ventilation), and particle properties (e.g., particle size, hygroscopicity, and solubility in airway fluids and cellular components). Inhalability is particularly important for between species extrapolation since it decreases more rapidly as particle size increases in rodents (commonly used in laboratory studies) compared to humans. In people, the fraction of oral versus nasal breathing is influenced by age, activity level, sex, disease status (e.g., allergies, upper respiratory

infections), and perhaps body mass index, which ultimately contributes to the fraction of particles inhaled and reaching the lower respiratory tract.

Recent evidence shows that in both humans and rodents, a small fraction of gold nanoparticles depositing in the peripheral lung may move into circulation. The fraction of deposited particles that move into circulation is dependent on particle size and is in the range of 0.2% or less for particles between 5 nm and 200 nm, but may reach a few percent for smaller particles. The translocated particles are distributed around the body and may be retained in other organs or eliminated via urine. Some more limited data show that particles may also reach the fetus in a size dependent manner. Although translocation in humans has only been demonstrated for gold nanoparticles and to some degree for titanium dioxide, the translocation of several types of nanoparticles has been demonstrated in rodents. The importance of compound type on particle translocation has not yet been ascertained. These studies suggest that, following deposition in the lung, a small fraction of ambient particles under 200 nm may translocate into circulation.

Health and Welfare Effects of PM Exposure

This ISA integrates information on PM exposure and health effects from epidemiologic, controlled human exposure, and toxicological studies to determine the causal nature of relationships between exposure to PM of various size fractions (i.e., $PM_{2.5}$, $PM_{10-2.5}$, and UFPs) and broad health effect categories. For most health effect categories, except for reproductive and developmental effects, effects are evaluated separately for short-term exposures (i.e., hours up to approximately one month) and long-term exposures (i.e., one month to years). For welfare effects the ISA evaluates evidence as it pertains to the welfare effects of visibility impairment, climate effects, and effects on materials. A consistent and transparent framework [Preamble to the ISA (U.S. EPA, 2015), Table II] is applied to classify the health and welfare effects evidence according to a five-level hierarchy:

1. Causal relationship
2. Likely to be a causal relationship
3. Suggestive of, but not sufficient to infer, a causal relationship
4. Inadequate to infer the presence or absence of a causal relationship
5. Not likely to be a causal relationship

The causality determinations presented in Table ES-1, reflect those PM size fraction, exposure duration, and broad health category combinations for which a "*causal relationship*" or "*likely to be causal relationship*" was concluded in this ISA. The conclusions presented are informed by recent findings in combination with the evidence detailed in the 2009 PM ISA. Important considerations include: (1) determining whether laboratory studies of humans and animals, in combination with epidemiologic studies, inform the biological mechanisms by which PM can impart health effects and provide evidence demonstrating that PM exposure can independently cause a health effect; (2) determining whether there is consistency in epidemiologic evidence across various geographic locations, populations, and methods

used to estimate PM exposure; (3) evaluating epidemiologic studies that examine potential influence of factors (i.e., confounders) that could bias associations observed with PM exposure; (4) determining the coherence of findings integrated across controlled human exposure, epidemiologic, and toxicological studies; and (5) making judgments regarding the influence of error and uncertainty on the relationship between PM exposure and health effects in the collective body of available studies. Table ES-2 details the causality determinations for the welfare effects.

Table ES-1 Summary of "causal relationship" and "likely to be causal relationship" causality determinations for PM exposure and health effects from the current draft PM ISA and corresponding causality determinations from the 2009 PM ISA.

Size Fraction	Health Effect Category[a] and Exposure Duration	Causality Determination	
		2009 PM ISA	Current Draft PM ISA
$PM_{2.5}$	Respiratory Effects—Short-term exposure Section 5.1.12, Table 5-18	Likely to be a causal relationship	Likely to be a causal relationship
	Respiratory Effects—Long-term exposure Section 5.2.13, Table 5-28	Likely to be a causal relationship	Likely to be a causal relationship
	Cardiovascular Effects—Short-term exposure Section 6.1.16, Table 6-33	Causal relationship	Causal relationship
	Cardiovascular Effects—Long-term exposure Section 6.2.18, Table 6-52	Causal relationship	Causal relationship
	Nervous System Effects—Long-term exposure Section 8.2.9, Table 8-20	Not evaluated	Likely to be a causal relationship
	Cancer—Long-term exposure Section 10.2.6, Table 10-8	Suggestive of, but not sufficient to infer, a causal relationship	Likely to be a causal relationship
	Total mortality—Short-term exposure Section 11.1.12, Table 11-4	Causal relationship	Causal relationship
	Total mortality—Long-term exposure Section 11.2.7, Table 11-8	Causal relationship	Causal relationship

Table ES-1 (Continued): Summary of "Causal Relationship" and "Likely to be Causal Relationship" causality determinations for PM exposure and health effects from the current draft PM ISA and corresponding causality determinations from the 2009 PM ISA.

Size Fraction	Health Effect Category[a] and Exposure Duration	Causality Determination	
		2009 PM ISA	Current Draft PM ISA
UFP	Nervous System Effects—Long-term exposure Section 8.6.7, Table 8-34	Not evaluated	Likely to be a causal relationship

ISA = Integrated Science Assessment; PM = particulate matter; $PM_{2.5}$ = fine particulate matter; UFP = ultrafine particles.

Previous causality determinations taken from the 2009 PM ISA (U.S. EPA, 2009).

[a]An array of outcomes is evaluated as part of a broad health effect category: physiological measures (e.g., airway responsiveness), clinical outcomes (e.g., hospital admissions), and cause-specific mortality. Total mortality includes all nonaccidental causes of mortality and is informed by findings for the spectrum of morbidity effects (e.g., respiratory, cardiovascular) that can lead to mortality. The sections and tables referenced include a detailed discussion of the evidence that supports the causality determinations and the $PM_{2.5}$ and UFP concentrations with which health effects have been associated.

Health Effects of $PM_{2.5}$ Exposure

Across the PM size fractions evaluated within this ISA, the most substantial scientific evidence indicating relationships between short- and long-term PM exposure is for $PM_{2.5}$. The causality determinations for $PM_{2.5}$ reflect the total body of scientific evidence, building off the conclusions presented in the 2009 PM ISA. The following sections detail those exposure duration and broad health effect categories where this ISA concluded a "*causal*" or "*likely to be causal*" causality determination, reflecting the highest degree to which the evidence reduces chance, confounding, and other biases in the exposure—health effect relationship. Those health effect categories where there is still a large degree of uncertainty or limited examination of the relationship between $PM_{2.5}$ exposure and health effects resulting in the causality determination of "*suggestive of, but not sufficient to infer, a causal relationship*" and "*inadequate to determine the presence or absence of a causal relationship*" are summarized in CHAPTER 1, Table 1-7.

Respiratory Effects

As in the 2009 PM ISA, the current ISA concludes there is a "*likely to be causal relationship*" between *short-term $PM_{2.5}$ exposure and respiratory effects* (Section 5.1). Recent epidemiologic studies continue to provide strong evidence for a relationship between short-term $PM_{2.5}$ exposure and several respiratory-related endpoints, including asthma exacerbation, chronic obstructive pulmonary disease (COPD) exacerbation, and combined respiratory-related diseases, particularly from studies examining emergency department visits and hospital admissions. The consistent, positive associations observed for asthma and COPD emergency department visits and hospital admissions are further supported by evidence of increased symptoms and medication use in response to short-term $PM_{2.5}$ exposure, which is

indicative of asthma and COPD exacerbations. Animal toxicological studies of short-term $PM_{2.5}$ exposure provide coherence and biological plausibility for asthma and COPD exacerbations by demonstrating asthma-related responses in an animal model of allergic airways disease and enhanced lung injury and inflammation in an animal model of COPD. Animal toxicological evidence also demonstrates altered host defense, greater susceptibility to bacterial infection, respiratory irritant effects, and other effects. This broad body of experimental evidence indicating $PM_{2.5}$-related respiratory effects in healthy populations generally provides biological plausibility for respiratory effects in association with short-term $PM_{2.5}$ exposure, but does not inform the relationship with asthma or COPD exacerbation. In addition, controlled human exposure studies provide minimal evidence of effects due to short-term $PM_{2.5}$ exposure, such as decrements in lung function and pulmonary inflammation. Recent epidemiologic studies build upon the limited number of studies that previously examined potential copollutant confounding and indicate that $PM_{2.5}$ associations with asthma exacerbation, combined respiratory-related diseases, and respiratory mortality remain relatively unchanged in copollutant models with gaseous pollutants (i.e., O_3, NO_2, SO_2, with more limited evidence for CO) and other particle sizes (i.e., $PM_{10-2.5}$). Animal toxicological studies further support an independent effect of $PM_{2.5}$ on respiratory health by demonstrating asthma- and COPD-related responses in animal models of disease. Evidence of consistent, positive associations between $PM_{2.5}$ and respiratory mortality demonstrate a continuum of respiratory-related effects.

Both the 2009 PM ISA, and the current ISA concluded there is a "*likely to be causal relationship*" between *long-term $PM_{2.5}$ exposure and respiratory effects* (Section 5.2). There is strong evidence from multiple cohorts that varied in study location, exposure assessment methods, and time periods examined that demonstrated an effect of long-term $PM_{2.5}$ exposure on lung development (i.e., lung function growth). Additional, although more limited, evidence from epidemiologic studies indicates associations between long-term $PM_{2.5}$ exposure and asthma development in children, asthma prevalence in children, childhood wheeze, and pulmonary inflammation. Animal toxicological studies demonstrating impaired lung development resulting from pre- and post-natal $PM_{2.5}$ exposure and the development of an allergic phenotype along with an increase in airway responsiveness following long-term $PM_{2.5}$ exposure provide biological plausibility for these findings. Animal toxicological studies also demonstrate $PM_{2.5}$ exposure-induced oxidative stress, inflammation, and morphological changes in both upper and lower airways. There is limited assessment of potential copollutant confounding of respiratory morbidity outcomes, but recent animal toxicological studies partially address the independence of $PM_{2.5}$ effects by demonstrating $PM_{2.5}$ induced oxidative stress, inflammation, and morphologic changes. This broad body of experimental evidence indicating $PM_{2.5}$-related respiratory effects in healthy populations generally provides biological plausibility for respiratory effects in association with long-term $PM_{2.5}$ exposure. Additional epidemiologic evidence, indicates an acceleration of lung function decline in adults, as well as consistent evidence for respiratory mortality and cause-specific respiratory mortality, providing evidence of a continuum of effects in response to long-term $PM_{2.5}$ exposure. The relationship between long-term $PM_{2.5}$ exposure and respiratory effects is further supported by epidemiologic studies demonstrating improvements in lung function growth and bronchitic symptoms in children and improvement in lung function in adults in association with declining $PM_{2.5}$ concentrations.

Cardiovascular Effects

Consistent with the 2009 PM ISA, this ISA concludes there is a "*causal relationship*" between *short-term $PM_{2.5}$ exposure and cardiovascular effects* (Section 6.1). The strongest evidence comes from epidemiologic studies that reported consistent, positive associations between short-term $PM_{2.5}$ exposure and cardiovascular-related emergency department visits and hospital admissions particularly for ischemic heart disease (IHD) and heart failure (HF), as well as cardiovascular-related mortality. Recent examinations of potential copollutant confounding generally indicate that the associations observed with $PM_{2.5}$ and cardiovascular effects in single pollutant models remain relatively unchanged in copollutant models, providing evidence that the observed associations with $PM_{2.5}$ are not artefacts due to confounding by another air pollutant. The independence of a $PM_{2.5}$ cardiovascular effect is further supported by recent experimental studies. Recent controlled human exposure studies expand upon previous findings and demonstrate $PM_{2.5}$-induced changes in endothelial function and blood pressure, which is coherent with animal toxicological studies demonstrating the same effects. Moreover, experimental evidence demonstrating decreased cardiac contractility and left ventricular pressure is coherent with epidemiologic studies observing positive associations between ambient $PM_{2.5}$ and ED visits and hospital admissions for HF. Thus, the collective body of experimental evidence supports and provides biological plausibility for epidemiologic studies reporting associations particularly between short-term $PM_{2.5}$ exposure and IHD and HF outcomes, as well as a range of other cardiovascular-related effects (e.g., arrhythmia, thrombosis) that can result in more severe outcomes possibly leading to death.

The 2009 PM ISA, as well as the current PM ISA, concluded there is a "*causal relationship*" between *long-term $PM_{2.5}$ exposure and cardiovascular effects* (Section 6.2). Epidemiologic studies of multiple recent U.S.-based cohorts along with reanalyses of these cohorts provide strong evidence of consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality. These studies used a variety of exposure assessment and statistical techniques and examined various spatial domains (e.g., 1 × 1 km grid cells, census tract, etc.) in many locations where mean annual average $PM_{2.5}$ concentrations are ≤12 μg/m^3. Recent epidemiologic studies of cardiovascular morbidity have greatly expanded upon the body of evidence available at the completion of the 2009 PM ISA by focusing on populations with distinct demographic characteristics (e.g., post-menopausal woman, male doctors, etc.) and extensively considering potential confounders (e.g., socioeconomic status [SES]). While an extended analysis of the Women's Health Initiative (WHI) cohort strengthened the initial observation of a relationship between long-term $PM_{2.5}$ exposure and coronary events among post-menopausal women, additional cohorts of women similar to the WHI cohort did not report consistent, positive associations with coronary heart disease (CHD), myocardial infarction or stroke. Longitudinal studies examining the progression of atherosclerosis in relation to long-term exposure to $PM_{2.5}$ reported inconsistent results that were dependent upon the vascular bed examined, but there was evidence of $PM_{2.5}$-associated coronary artery calcification, a strong predictor of CHD, within a study focusing on the progression of atherosclerosis in a healthy population, i.e., Multi-Ethnic Study of Arthrosclerosis and Air Pollution (MESA—Air). A limited number of epidemiologic studies examining other cardiovascular effects,

provide some evidence of associations with HF, blood pressure, and hypertension as well as subclinical cardiovascular biomarkers. Recent studies also reduce the uncertainty associated with potential copollutant confounding by reporting that associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality remained relatively unchanged or increased in copollutant models adjusted for O_3, NO_2, SO_2, and $PM_{10-2.5}$. Evidence from animal toxicological studies further supports a direct $PM_{2.5}$ effect on the cardiovascular system and provides coherence with effects observed in epidemiologic studies. For example, animal toxicological studies demonstrating atherosclerotic plaque progression in mice is coherent with epidemiologic studies of atherosclerosis, while animal toxicological studies reporting increased coronary artery wall thickness, decreased cardiac contractility and output, and changes in blood pressure are coherent with epidemiologic studies of HF. Furthermore, when considering the collective body of evidence there are biologically plausible pathways by which long-term exposure to $PM_{2.5}$ could lead to a continuum of effects potentially resulting in death.

Nervous System Effects

The 2009 PM ISA did not make a causality determination for long-term $PM_{2.5}$ exposure and nervous system effects due to the paucity of data available. Since the 2009 PM ISA, the literature base has greatly expanded and the combination of animal toxicological and epidemiologic evidence supports a "*likely to be causal relationship*" between *long-term $PM_{2.5}$ exposure and nervous system effects* (Section 8.2). Animal toxicological studies provide evidence for a range of nervous system effects including neuroinflammation and oxidative stress, neurodegeneration, cognitive effects, and effects on neurodevelopment. Epidemiologic studies, although fewer in number, generally support associations between long-term $PM_{2.5}$ exposure and changes in brain morphology, cognitive decrements, and dementia. Both experimental and epidemiologic evidence is well substantiated and coherent, supporting a pathway involving neuroinflammation in specific regions of the brain (i.e., the hippocampus, cerebral cortex and hypothalamus) and morphologic changes in the brain indicative of neurodegeneration. Overall, the lack of consideration of copollutant confounding introduces some uncertainty in the interpretation of the epidemiologic studies but this uncertainty is addressed, in part, by the direct evidence of effects provided by experimental animal studies. In addition to the nervous system effects primarily observed in adults, there is initial and limited epidemiologic evidence of neurodevelopmental effects, specifically autism spectrum disorder (ASD), which is supported by an animal toxicological study demonstrating $PM_{2.5}$-induced inflammatory and morphologic changes in regions of the brain consistent with ASD.

Cancer

The 2009 PM ISA concluded that evidence was "*suggestive of a causal relationship*"[30] between *long-term $PM_{2.5}$ exposure and cancer* (Section 10.2). Building upon the decades of research on whole PM

[30] Since the 2009 PM ISA, the causality determination language has been updated and this category is now stated as "suggestive of, but not sufficient, to infer a causal relationship".

exposures and evidence presented in the 2009 PM ISA, recent experimental and epidemiologic evidence indicating genotoxicity, epigenetic effects (i.e., hypo- and hyper-methylation of DNA), and increased carcinogenic potential due to $PM_{2.5}$ exposure, along with strong epidemiologic evidence for increases in lung cancer incidence and mortality supports a "*likely to be causal relationship*" between long-term $PM_{2.5}$ exposure and cancer. $PM_{2.5}$ exhibits various characteristics of carcinogens, as shown in studies demonstrating genotoxic effects (e.g., DNA damage), epigenetic alterations, oxidative stress, and electrophilicity. Studies of cancer development have often focused on whole PM exposures[31], not individual PM size fractions, or individual components often found to encompass $PM_{2.5}$ (e.g., hexavalent chromium, arsenic). Ames *Salmonella*/mammalian-microsome mutagenicity assays of $PM_{2.5}$ and $PM_{2.5}$ extracts demonstrate that PM contains mutagenic agents. In vitro and in vivo toxicological studies demonstrate the potential for $PM_{2.5}$ exposure to result in DNA damage, which is supported by limited human evidence. Cytogenic effects (e.g., chromosomal aberrations), and differential expression of genes potentially relevant to genotoxicity or cancer pathogenesis have also been demonstrated. There is also limited evidence for cellular and molecular changes that could lead to genomic instability as well as for the carcinogenic potential of $PM_{2.5}$, as demonstrated by enhanced tumor formation in animals treated with urethane. The experimental and epidemiologic evidence of genotoxicity, epigenetic effects, and carcinogenic potential provides biological plausibility for the results from multiple epidemiologic studies conducted in diverse cohorts in terms of geographic coverage and population demographics reporting primarily consistent, positive associations between long-term $PM_{2.5}$ exposure and lung cancer incidence and mortality, particularly in never smokers. In the limited assessment of potential copollutant confounding, $PM_{2.5}$-lung cancer incidence and mortality associations were found to be relatively unchanged in models with O_3.

Mortality

As in the 2009 PM ISA, the current ISA concludes there is a "*causal relationship*" between *short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality* (Section 11.1). Recent multicity studies conducted in the U.S., Canada, Europe, and Asia in combination with the single- and multicity studies evaluated in the 2009 PM ISA continue to provide evidence of consistent, positive associations between short-term $PM_{2.5}$ exposure and total mortality. The positive associations reported across studies reflect both traditional analyses using ambient monitors as well as analyses conducted in both urban and rural locations that use new exposure assignment techniques and rely on multiple sources of $PM_{2.5}$ data (e.g., ambient monitors, statistical models, and satellite images). Recent studies also expand upon the assessment of potential copollutant confounding and indicate that $PM_{2.5}$-mortality associations are relatively unchanged in copollutant models with gaseous pollutants and $PM_{10-2.5}$. The positive associations reported for total mortality are supported by positive associations for cause-specific mortality (i.e., cardiovascular- and respiratory-related mortality). The consistent and coherent evidence across

[31] Whole PM exposures represent exposures that contain both PM and gaseous pollutants.

scientific disciplines for cardiovascular morbidity, particularly ischemic events and HF (CHAPTER 6), and to a lesser degree for respiratory morbidity, with the strongest evidence for exacerbations of COPD and asthma (CHAPTER 5), provide biological plausibility for cause-specific mortality and ultimately total mortality. Recent studies also further reduce chance, confounding, and other biases in the relationship between short-term $PM_{2.5}$ exposure and total mortality.

Both the 2009 PM ISA and the current ISA concludes there is a "*causal relationship*" between *long-term $PM_{2.5}$ exposure and total (nonaccidental) mortality* (Section 11.2). Additional reanalyses and extensions of the American Cancer Society and Harvard Six Cities cohorts as well as new cohorts consisting of Medicare participants, people that live in Canada, or people employed in a specific job (e.g., teacher, nurse, etc.) further support a positive association between long-term $PM_{2.5}$ exposure and total mortality, particularly in areas with annual mean concentrations <20 $\mu g/m^3$, and in some cases below 12 $\mu g/m^3$. Positive associations persist regardless of the exposure assignment approach used (i.e., ambient monitors or the combination of monitoring, modeling, and satellite data) and in copollutant models, particularly with O_3 and more limited evidence for NO_2 and $PM_{10-2.5}$. The evidence for total mortality is supported by positive associations for cause-specific mortality, including cardiovascular, respiratory, and lung cancer mortality. The coherence of effects across scientific disciplines for cardiovascular morbidity, particularly for CHD, stroke and atherosclerosis, and respiratory morbidity for the development of COPD, contribute to the biological plausibility for mortality due to long-term $PM_{2.5}$ exposure. Additionally, recent studies demonstrating increases in life expectancy due to decreases in long-term $PM_{2.5}$ concentrations further support a relationship between long-term $PM_{2.5}$ exposure and total mortality.

Health Effects of UFP Exposure

Since the completion of the 2009 PM ISA recent studies further explored the relationship between UFP exposure and health effects. The interpretation of epidemiologic study results is complicated by most studies relying on a single monitor to measure UFPs, which is inadequate as has been reflected in some monitoring campaigns that demonstrate a high degree of spatial variability in UFP concentrations and that the size distribution of UFPs changes with distance from source (Section 2.5). Additionally, experimental studies often include size ranges up to 200 nm or higher, which complicates the examination of coherence and biological plausibility of UFP-related health effects. These uncertainties in addition to the inconsistency across studies in the characterization of UFP with respect to size distribution and exposure metric contributed to causality determinations that did not exceed "*suggestive of, but not sufficient to infer, a causal relationship*" for most exposure and health effect category combinations.

Nervous System Effects

Due to the few studies that examined long-term UFP exposure and nervous system effects, the 2009 PM ISA did not make a causality determination; however, it was hypothesized that ambient UFPs may reach the brain via olfactory transport based on a few animal toxicological studies of

laboratory-generated UFPs. Since then, additional strong animal toxicological evidence of neurotoxicity and altered neurodevelopment, in combination with initial evidence suggesting potential translocation of UFPs into the brain via olfactory transport and from a single epidemiologic study indicating effects on attention and memory support a "*likely to be causal relationship*" between *long-term UFP exposure and nervous system effects* (Section 8.6). Animal toxicological studies provide consistent evidence of brain inflammation and oxidative stress in multiple regions of the brain, morphologic changes that are characteristic of neurodegeneration and Alzheimer's disease. Additionally, there is evidence of neurodevelopmental effects, including behavioral, neuroinflammatory, and morphological changes consistent with ASD. The animal toxicological study results are supported by an epidemiologic study reporting evidence of decrements on tests of attention and memory in children. However, epidemiologic studies of long-term UFP exposure are sparse due to difficulties in capturing the spatial variation in long-term UFP concentrations that can result in substantial exposure measurement error.

Policy-Relevant Considerations for Health Effects Associated with Particulate Matter Exposure

This section describes issues relevant for considering the potential significance of impacts of ambient PM, particularly $PM_{2.5}$, exposure on public health (Section 1.6)[32], including potential copollutant confounding of $PM_{2.5}$-health effects associations, the relationship between $PM_{2.5}$ exposure and the timing of health effects, the shape of the concentration-response (C-R) relationship, whether $PM_{2.5}$ components and sources are more closely associated with health effects than $PM_{2.5}$ mass, and the identification of populations and lifestages potentially at increased risk of a $PM_{2.5}$-related health effect.

Recent epidemiologic studies greatly expand upon the evidence informing whether associations observed between short- and long-term $PM_{2.5}$ exposure and health are confounded by other pollutants observed in the air pollution mixture. The examination of potential copollutant confounding in studies of respiratory and cardiovascular effects are primarily limited to studies of emergency department visits and hospital admissions. Across studies of short-term $PM_{2.5}$ exposure and respiratory and cardiovascular effects and mortality, correlations between $PM_{2.5}$ and gaseous (i.e., SO_2, NO_2, CO, and O_3) and particulate pollutants (i.e., $PM_{10-2.5}$) varied across studies, with low-to-moderate correlations (i.e., <0.7). Collectively, studies of short-term $PM_{2.5}$ exposure that examined potential copollutant confounding indicated that associations remained relatively unchanged in copollutant models, and in instances where associations were attenuated they remained positive. Far fewer studies examined potential copollutant confounding and long-term $PM_{2.5}$ exposure, but there has been an expansion of studies focusing on mortality. Studies focusing on respiratory (i.e., lung function and asthma development) and cardiovascular effects (i.e., cardiovascular mortality), along with lung cancer incidence and mortality, provide initial evidence that associations with $PM_{2.5}$ are relatively unchanged in copollutant models with primarily traffic-related pollutants (i.e., NO_2, NO_X, and CO) and O_3. For mortality, the most extensive

[32] Section 1.6 in Chapter 1 integrates the evidence across all health chapters, but each health chapter has individual discussions on the topics discussed within this section.

analyses occurred for O_3, with more limited assessments of other pollutants, but overall associations were reported to remain unchanged in copollutant models for total (nonaccidental) mortality, cardiovascular, and respiratory mortality.

An important question that informs different aspects of the PM NAAQS is the timing of observed effects due to short-term $PM_{2.5}$ exposure, specifically the averaging time of the exposure metric in epidemiologic studies and the lag days over which health effects are observed. Some recent epidemiologic studies focusing on respiratory- and cardiovascular-related emergency department visits and hospital admissions, cardiovascular effects (e.g., ST-elevation, myocardial infarction, and out-of-hospital cardiac arrest), and mortality examined associations between subdaily exposure metrics and the widely used 24-hour average exposure metric. Across the studies evaluated, the available evidence does not indicate that sub-daily averaging periods for $PM_{2.5}$ are more closely associated with health effects than the 24-hour average exposure metric. In addition to examining potential differences in associations by averaging time of the exposure metric, recent epidemiologic studies expanded the assessment of examining the timing of effects by systematically examining lag days by focusing on whether there is evidence of an immediate (e.g., lag 0–1 days), delayed (e.g., lag 2–5 days), or prolonged (e.g., lag 0–5 days) effect of PM on health. Epidemiologic studies examining potential differences in associations in relation to short-term $PM_{2.5}$ exposure focused on respiratory- and cardiovascular-related emergency department visits and hospital admissions as well as mortality. While recent studies provided evidence of associations in the range of 0–5 days for respiratory effects, there was evidence of an immediate effect for cardiovascular effects and mortality (i.e., 0–1 days) with some initial evidence of associations occurring over longer exposure durations (e.g., 0–4 days).

An examination of the C-R relationship between short- and long-term $PM_{2.5}$ exposure and health effects can inform both the shape of the C-R curve and whether there is a threshold (i.e., concentration level) below which there is no evidence of an effect of $PM_{2.5}$ on health. Studies of short-term $PM_{2.5}$ exposure and health are limited to studies of respiratory-related emergency department visits and hospital admissions, and mortality. Epidemiologic studies of respiratory disease and asthma emergency department visits and hospital admissions focusing on the shape of the C-R curve provide initial evidence of a linear relationship with less certainty at concentrations below 10 $\mu g/m^3$. However, studies focusing on whether the $PM_{2.5}$ association changes at different concentration ranges (i.e., cut-point analyses) provide some evidence of potential nonlinearities in the C-R relationship. Epidemiologic studies of mortality greatly expand upon the evidence evaluated in the 2009 PM ISA where C-R analyses were limited to studies of PM_{10}. Evidence from U.S. studies examining short-term $PM_{2.5}$ exposure and mortality indicate a linear relationship at concentrations as low as 5 $\mu g/m^3$ with cut-point analyses providing no evidence of a threshold. For long-term $PM_{2.5}$ exposure, most of evidence on the shape of the C-R curve and whether a threshold exits comes from studies of mortality with some initial recent evidence from studies of respiratory and cardiovascular effects, as well as lung cancer mortality and incidence. Epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality used a variety of statistical approaches and cut-point analyses, which support a linear, no-threshold relationship for total

(nonaccidental) mortality, especially at lower ambient $PM_{2.5}$ concentrations, with confidence in some studies in the range of 5–8 $\mu g/m^3$. Additionally, there is initial evidence indicating that the slope of the C-R curve may be steeper (supralinear) at lower concentrations for cardiovascular mortality. Evaluation of the C-R relationship is more limited for respiratory and cardiovascular effects, but overall initial assessments support a linear relationship specifically at long-term $PM_{2.5}$ concentrations ranging from 10 to 12 $\mu g/m^3$ and 5–10 $\mu g/m^3$, respectively.

Recent epidemiologic and experimental studies extensively build upon those studies evaluated in the 2009 PM ISA that examined relationships between exposure to $PM_{2.5}$ components and sources and health effects. As detailed in the Preface , this ISA focuses on specific study criteria to thoroughly evaluate whether there is evidence that an individual component(s) and/or source(s) is more closely related to health effects than PM mass. Across the health effects categories evaluated in this ISA, most studies that examine PM sources and components focused on $PM_{2.5}$. In studies examining both short- and long-term exposure a variety of health effects were examined ranging from subclinical (e.g., changes in lung function, respiratory symptoms) to more overt e.g., emergency department visits, hospital admissions, and mortality). Across exposure durations and health effects categories it was concluded that many $PM_{2.5}$ components and sources are associated with many health effects, and the evidence does not indicate that any one source or component is consistently more strongly related with health effects than $PM_{2.5}$ mass.

Lastly, an important consideration in evaluating whether the NAAQS provides public health protection with an adequate margin of safety is assessing whether there are specific populations or lifestages at increased risk of a PM-related health effect. While the ISA provides substantial evidence of health effects due to short- and long-term exposure to $PM_{2.5}$ across populations with diverse characteristics (e.g., children, older adults, people with pre-existing cardiovascular diseases, etc.), an evaluation of whether any of these populations are at increased risk of a PM-related health effect relies on evidence from specific types of studies that can directly inform this question as detailed in Section 1.6 and CHAPTER 12. Based on the framework for characterizing the evidence for populations potentially at increased risk of an air pollutant-related health effect detailed in the 2013 O_3 ISA (U.S. EPA, 2013), this ISA concludes there is adequate evidence that children are at increased risk of a $PM_{2.5}$-related health effect based off strong evidence of impaired lung function growth and additional evidence of decrements in lung function and asthma development. Additionally, there is adequate evidence that nonwhite people are at increased of $PM_{2.5}$-related health effects based on studies of long-term $PM_{2.5}$ exposure and mortality and studies demonstrating differential exposure by race. There was also suggestive evidence that populations with pre-existing cardiovascular and respiratory disease, that are overweight or obese, with genetic variants in genes in the glutathione pathway and oxidant metabolism, or that are of low SES are at increased risk for $PM_{2.5}$-related health effects.

PM Exposure and Welfare Effects

Compared to the evaluation of the health effects evidence, the evaluation of the welfare effects evidence focuses broadly on PM and not individual size fractions or exposure durations. Additionally, the evaluation, as noted previously, focuses on the welfare effects of visibility impairment, climate effects, and effects on materials due to the ecological effects of PM being evaluated in the ISA for Oxides of Nitrogen, Oxides of Sulfur and Particulate Matter–Ecological Criteria (U.S. EPA, 2018).

Table ES-2 Summary of causality determinations for relationships between PM exposure and welfare effects from the 2009 and current draft PM ISA.

Welfare Effect Category	Causality Determination	
	2009 PM ISA	Current Draft PM ISA
Visibility Impairment Section 5.1.12, Table 5-18	Causal relationship	Causal relationship
Climate Effects Section 5.2.13, Table 5-28	Causal relationship	Causal relationship
Effects on Materials Section 6.1.16, Table 6-33	Causal relationship	Causal relationship

ISA = Integrated Science Assessment; PM = particulate matter.
Previous causality determinations taken from the 2009 PM ISA (U.S. EPA, 2009).

As noted in Table ES-2, this ISA concludes a "causal relationship" between PM visibility impairment, climate effects, and effects on materials which is consistent with the 2009 PM ISA. For visibility impairment (Section 13.2), the relationship between PM and light extinction has been well characterized. The rapid decline in $PM_{2.5}$ sulfate that has occurrent from 2002−2012 (i.e., −4.6% per year in rural areas and −6.2% per year in urban areas) has contributed to improvements in visibility in many areas, but an increasing amount of light extinction is now due to nitrate and organic matter. There have been no recent visibility preference studies; however, a recent meta-analysis demonstrates that scene-dependent haze metrics better account for preference compared to only using the deciview scale as a metric. For climate (Section 13.3), there is substantial evidence indicating that PM affects the radiative forcing of the climate system, both through direct scattering and absorption of radiation, and indirectly, by altering cloud properties. However, it is important to note there are still substantial uncertainties with respect to key processes linking PM and climate, specifically clouds and aerosols because of the scale between PM-relevant cloud processes and the resolution of state-of-the-art models and the indirect impacts and feedbacks in the climate system due to an initial radiative effect due to PM. Lastly, for effects on materials (Section 13.4), most of the evidence has often focused on examining PM impacts on stone

used for historic monuments and buildings. Recent evidence further expands the understanding of soiling and corrosion process for glass and metals, and demonstrates that atmospheric soiling can impact energy efficiency of photovoltaic systems and some buildings.

Scientific Considerations and Key Findings of the Health and Welfare Effects Evidence

As summarized in the Preface (Section P.3), the Preamble to the ISAs (U.S. EPA, 2015) describes the process by which the U.S. EPA evaluates the strengths and limitations in the scientific evidence using a weight-of-evidence framework to form causality determinations within the ISAs. There are five different causality determinations, which may be used to characterize evidence with each determination delineated by the degree to which chance, confounding, and other biases affect interpretation of the scientific evidence (Table P-2). As documented by the extensive evaluation of evidence throughout the subsequent chapters of this ISA, the U.S. EPA carefully considers uncertainties in the evidence, and the extent to which recent studies have addressed or reduced uncertainties from previous assessments, as well as the strengths of the evidence. Uncertainties considered in the epidemiologic evidence, for example, include the potential for confounding by copollutants or covarying factors and exposure error. The U.S. EPA evaluates many other important considerations (not uncertainties) such as coherence of evidence from animal and human studies, evaluation of different PM components, heterogeneity of risk estimates, and the shape of concentration-response relationships. All aspects are evaluated in drawing scientific conclusions and making causality determinations, and where there is clear evidence linking PM with effects with minimal remaining uncertainties, the U.S. EPA makes a determination of a *causal* or *likely to be causal* relationship.

Key findings of the health effects evidence spanning each of the PM size fractions and welfare effects evaluated in this ISA are summarized below and in Chapter 1 (Section 1.7). These highlights encapsulate the evidence that informed consideration of strengths and limitations and development of causality determinations. For the health (i.e., respiratory and cardiovascular effects, and mortality due to short- and long-term $PM_{2.5}$ exposure) or welfare effects categories for which *causal* or *likely to be causal* determinations were made, recent findings were found to reduce or fully address previous uncertainties in the evidence and increase the strength of U.S. EPA's scientific conclusions. For other PM-effect relationships, the key findings highlighted below indicate where there is strength in the evidence, but uncertainties remain, resulting in causality determinations of *suggestive of, but not sufficient to infer, a causal relationship* or in some cases *inadequate to infer the presence or absence of a causal relationship*, both of which reflect there is limited evidence to evaluate both strengths and weaknesses.

Health Effects Evidence: Key Findings

A large body of scientific evidence spanning many decades clearly demonstrates there are health effects attributed to both short- and long-term PM exposure, with the strongest evidence for a relationship between some health effects and $PM_{2.5}$. Generally, for most health effects and exposures to $PM_{10-2.5}$ and UFPs, there are more limitations and uncertainties across scientific disciplines (i.e., atmospheric chemistry, exposure science, and both epidemiology and experimental sciences), complicating the interpretation of the evidence. The collective body of evidence for each of the PM size fraction, exposure, and health outcome category combinations evaluated in this ISA was carefully considered and assessed, including the inherent strengths, limitations, and uncertainties in the overall body of evidence such as the available methods, models and data used within and across studies. This full assessment of the current state of the science for $PM_{2.5}$, $PM_{10-2.5}$, and UFPs resulted in the causality determinations detailed in Table 1-4. Through identification of the strengths and limitations in the evidence this ISA may help in the prioritization of research efforts to support future PM NAAQS reviews. Examples of the key findings in the health effects evidence considered in this PM ISA include:

$PM_{2.5}$

- There are many recent epidemiologic studies conducted in diverse geographic locations, encompassing different population demographics, and using a variety of exposure assignment techniques, that continue to report consistent positive associations between short- and long-term $PM_{2.5}$ exposure and respiratory and cardiovascular effects and mortality. This evidence continues to support the large body of previously published epidemiologic studies reporting positive $PM_{2.5}$ associations with respiratory and cardiovascular effects and mortality and in some cases strengthens and extends the evidence base for other health effects.
- New $PM_{2.5}$ exposure assignment methods that utilize several sources of available data (i.e., satellite observations, model predictions, and ambient monitors) in epidemiologic studies better allow for the inclusion of less urban areas. These methods are well validated by $PM_{2.5}$ monitors in areas with moderate-to-high population density. Although fewer monitors are available for model validation in sparsely populated rural areas compared with urban areas, $PM_{2.5}$ concentrations are typically lower and more spatially homogeneous in rural areas, resulting in the need for fewer validation sites.
- The large number of animal toxicological and controlled human exposure studies provide coherence and biological plausibility for effects observed, particularly respiratory, cardiovascular, and mortality in epidemiologic studies of short- and long-term $PM_{2.5}$ exposure.
- Both animal toxicological and controlled human exposure studies, using concentrated ambient particle (CAP) exposures, provide evidence of a direct effect of PM exposure on various health effects.
- Epidemiologic studies that conducted copollutant analyses show that associations remain relatively unchanged when adjusting for gaseous pollutants and other particle size fractions (e.g., $PM_{10-2.5}$), addressing a key uncertainty identified in the 2009 PM ISA.
- Recent epidemiologic studies indicate that the observed heterogeneity in risk estimates is not attributed solely to differences in the composition of $PM_{2.5}$, but also reflects city-specific exposure conditions (e.g., housing and commuting characteristics).

- Evidence continues to support a linear, no-threshold concentration—response relationship, but with less certainty in the shape of the curve at lower concentrations (i.e., below about 8 $\mu g/m^3$).
- For health effects where it was concluded that the evidence is suggestive of, but not sufficient to infer, a causal relationship (including short- and long-term $PM_{2.5}$ exposure and metabolic effects, male and female reproduction and fertility, pregnancy and birth outcomes, and short-term exposures and nervous system effects) epidemiologic and experimental studies report inconsistent evidence of an association/effect or there are relatively few studies focusing on the health effect of interest.

$PM_{10-2.5}$

- Routine national monitoring of $PM_{10-2.5}$ was initiated in 2011. $PM_{10-2.5}$ concentrations are more spatially and temporally variable than $PM_{2.5}$. Although some $PM_{10-2.5}$ data are available across the nation, micro-to-neighborhood scale data are not widely available, adding uncertainty to the interpretation of results from epidemiologic studies, especially for long-term exposure studies that rely on spatial contrasts to examine associations with health effects.
- Epidemiologic studies that examined associations between short- and long-term $PM_{10-2.5}$ exposure and various health effects use multiple methods to estimate concentrations, complicating the comparison of results across studies.
- Depending on the health effect, few or no experimental studies examined the relationship between short- and long-term exposure to $PM_{10-2.5}$ and health effects. The few studies conducted provide inconsistent evidence of effects due to $PM_{10-2.5}$ exposures contributing to limited coherence and biological plausibility.
- The causality determinations for all health outcome categories for short- and long-term $PM_{10-2.5}$ exposure were either *suggestive of, but not sufficient to infer, a causal relationship* or *inadequate to infer the presence or absence of a causal relationship*, indicating limitations and uncertainties in the evidence base.

UFPs

- There is no national ambient monitoring network in place to measure UFP concentrations, thus there is limited information on UFP exposures within the U.S.
- There are a limited number of epidemiologic studies that examined short- or long-term UFP exposure and various health effects.
- It is difficult to assess the results across epidemiologic studies due to the different size ranges of UFPs examined, the exposure metrics used, and spatial and temporal variability of UFP concentrations.
- There is strong and consistent animal toxicological evidence linking long-term UFP exposure to nervous system effects, which directly informed the *likely to be causal relationship* conclusion. This evidence is in contrast to the limited evidence base for other health effects.
- For all other health effect categories, animal toxicological studies and controlled human exposure studies provide limited, and in some instances inconsistent, evidence of effects due to short- or long-term UFP exposure contributing to limited coherence and biological plausibility.
- There is evidence of translocation of UFPs to the brain via the olfactory nerve, but it is unclear whether this translocation occurs in humans as well as in animals. There is also uncertainty surrounding the mechanisms and degree to which particles translocate from the respiratory tract

to the brain, however, translocation of particles to the brain may not be required for UFP-related nervous system effects.

- For health effects where it was concluded that the evidence is *inadequate to infer the presence or absence of a causal relationship*, few or no epidemiologic and experimental studies examined the relationship between short- or long-term UFP exposures.

Welfare Effects Evidence: Key Findings

A large body of scientific evidence spanning many decades also demonstrates there are welfare effects attributed to PM. This collective body of evidence contributed to the causality determinations detailed in CHAPTER 13 of this ISA for each of the nonecological welfare effects evaluated (see Table 1-4). Examples of the key findings in the welfare effects evidence considered in this PM ISA include:

- Recent studies further confirm evidence from previous assessments supporting the strong relationship between PM and the nonecological welfare effects of visibility impairment, effects on the climate, and materials damage.
- For visibility impairment and materials damage there is extensive evidence demonstrating the relationship between PM and light extinction and PM impacts on stone, respectively.
- While there is substantial evidence indicating that PM affects the climate system, specifically through radiative forcing, there are still substantial uncertainties in key processes, such as the relationship between clouds and aerosols and the indirect impacts and feedbacks in the climate system due to the radiative effect of PM.

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CHAPTER 1 INTEGRATED SYNTHESIS

Overall Conclusions of the Particulate Matter (PM) Integrated Science Assessment (ISA)

- Recent evidence spanning the scientific disciplines (i.e., atmospheric chemistry, exposure science, dosimetry, epidemiology, controlled human exposure, and animal toxicology) builds upon evidence detailed in the 2009 PM ISA and reaffirms that for short- and long-term $PM_{2.5}$ exposure there is a "*causal relationship*" for cardiovascular effects and total (nonaccidental) mortality and a "*likely to be causal relationship*" for respiratory effects.
- Recent experimental and epidemiologic evidence supports a "*likely to be causal relationship*" for long-term $PM_{2.5}$ exposure and nervous system effects.
- Recent evidence, primarily from studies of lung cancer incidence and mortality, in combination with the decades of research on the mutagenicity and carcinogenicity of PM supports a "*likely to be causal relationship*" between long-term $PM_{2.5}$ exposure and cancer.
- Recent evidence from primarily animal toxicological studies supports a "*likely to be causal relationship*" for long-term ultrafine particle (UFP) exposure and nervous system effects.
- Remaining uncertainties and limitations in the scientific evidence contribute to a "*suggestive of, but not sufficient to infer,* a *causal relationship*" and "*inadequate to infer the presence or absence of a causal relationship*" for all other exposure, size fraction, and health effects combinations.
- Recent evidence builds upon and reaffirms that there is a "*causal relationship*" between PM and the nonecological welfare effects: visibility impairment, climate effects, and materials effects.
- The assessment of PM sources and components confirms and continues to support the conclusion from the 2009 PM ISA: *Many $PM_{2.5}$ components and sources are associated with many health effects, and the evidence does not indicate that any one source or component is more strongly related with health effects than $PM_{2.5}$ mass.*
- Many populations (e.g., healthy, diseased, etc.) and lifestages (e.g., children, older adults, etc.) have been shown to be at-risk of a health effect in response to short- or long-term PM exposure, particularly $PM_{2.5}$. However, of the populations and lifestages examined, current scientific evidence indicates that only some populations may be at *disproportionately increased risk* of a $PM_{2.5}$-related health effect, including nonwhite populations, children, people with specific genetic variants in genes in the glutathione pathway, people who are overweight or obese, people with pre-existing cardiovascular and respiratory diseases, and people of low socioeconomic status (SES).

1.1 Introduction

1.1.1 Purpose

The subsequent chapters of this ISA provide a detailed evaluation and characterization of the current state of the science with respect to the health and nonecological welfare effects[33] due to exposure to particulate matter (PM). The overall scope of the ISA, which governs the types of studies considered in the evaluation of the scientific evidence, is detailed in the Preface . Aspects specific to evaluating studies of PM that form the basis of the causality determinations detailed within this ISA are described in the Appendix. The main chapters of the ISA provide both the scientific basis for causality determinations[34] and policy-relevant scientific information that supports the review of the National Ambient Air Quality Standards (NAAQS) for PM. The purpose of this CHAPTER 1 is not to summarize each of the chapters, but to synthesize the key findings on each topic considered in characterizing PM exposure and relationships with health and welfare effects. This ISA draws forward and integrates evidence evaluated in prior assessments including the 2009 PM ISA (U.S. EPA, 2009) and earlier assessments e.g., 2004 PM Air Quality Criteria Document (AQCD) (U.S. EPA, 2004) and 1996 PM AQCD (U.S. EPA, 1996).

1.1.2 Organization of the ISA

The ISA consists of the Preface (legislative requirements and history of the primary and secondary PM NAAQS; and purpose and overview of the ISA along with the overall scope, and process for evaluating evidence), Executive Summary, and thirteen chapters. CHAPTER 1 synthesizes the scientific evidence that best informs the policy-relevant questions detailed within the *Integrated Review Plan for the Primary National Ambient Air Quality Standards for Particulate Matter* (PM IRP; (U.S. EPA, 2016)) that frame this review of the primary (health-based) and secondary (welfare-based) PM NAAQS. CHAPTER 2 characterizes the sources, atmospheric processes related to PM formation, and trends in ambient PM concentrations, for specifically $PM_{2.5}$ (fine PM; PM with a nominal mean aerodynamic diameter less than or equal to 2.5 μm), $PM_{10-2.5}$ (thoracic coarse or coarse PM; PM with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm), and ultrafine particles [UFPs, generally considered as particulates with a diameter less than or equal to 0.1 μm (typically based on physical size, thermal diffusivity or electrical mobility)]. CHAPTER 3 describes methods to estimate human exposure to PM and the impact of exposure measurement error on

[33] Hereafter welfare effects refers to nonecological welfare effects, unless otherwise noted. The ecological effects resulting from the deposition of PM and PM components are being considered in a separate assessment as part of the review of the secondary (welfare-based) NAAQS for oxides of nitrogen, oxides of sulfur, and PM (U.S. EPA, 2018)

[34] The general process for developing an ISA, including the framework for evaluating weight of evidence and drawing scientific conclusions and causal judgments, is described in a companion document, Preamble to the Integrated Science Assessments (U.S. EPA, 2015).

associations with health effects. CHAPTER 4 describes the dosimetry of the various size fractions of PM. CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11 evaluate and integrate epidemiologic, controlled human exposure, and animal toxicological evidence and characterize the biological plausibility for health effects related to short-term and long-term exposure to $PM_{2.5}$, $PM_{10-2.5}$, and UFPs for respiratory effects, cardiovascular effects, metabolic effects, nervous system effects, reproductive and developmental effects, cancer, and mortality, respectively. CHAPTER 12 evaluates the scientific evidence on populations and lifestages potentially at increased risk of a PM-related health effect. Lastly, CHAPTER 13 evaluates the scientific evidence for welfare effects, focusing specifically on the nonecological welfare effects of visibility impairment, climate effects, and effects on materials.

A key consideration in the health effects assessment is the extent to which evidence indicates that $PM_{2.5}$, $PM_{10-2.5}$, and UFPs exposures independently cause health effects. To that end, this chapter draws upon information about the sources, atmospheric chemistry, distribution, background sources of ambient PM, as well as exposure to ambient PM of different size fractions and identifies pollutants and other factors related to the distribution of or exposure to ambient PM that can potentially influence epidemiologic associations observed between health effects and $PM_{2.5}$, $PM_{10-2.5}$, and UFP exposures (Section 1.2). The chapter also summarizes information on the dosimetry of inhaled PM of different size fractions (Section 1.3). The discussions of the health effects evidence and causality determinations (Section 1.4) details the extent to which there is biological plausibility for the various PM exposure duration-health effects relationships evaluated, and provides an integrated summary of the epidemiologic and experimental (i.e., animal toxicological and controlled human exposure) evidence and whether it collectively supports independent relationships between $PM_{2.5}$, $PM_{10-2.5}$, or UFPs exposure and health effects.[35] This chapter also integrates evidence across the ISA for specific policy-relevant issues that are informative in the PM NAAQS review (Section 1.5), specifically: potential copollutant confounding (Section 1.5.1); the timing of effects, which includes the lag structure of associations and averaging time for exposure metrics (Section 1.5.2); the shape of the concentration-response relationship and whether a threshold exits (Section 1.5.3); and whether individual PM components or exposure metrics representative of PM sources are a better indicator for the PM-health effects relationship than PM mass (Section 1.5.4). Additionally, within the policy-relevant considerations discussion, this chapter summarizes the evidence as to whether specific populations or lifestages are at increased risk of a PM-related health effect, which is an important consideration in the context of the NAAQS and ensuring public health is protected with an adequate margin of safety (Section 1.5.5). This chapter also characterizes the welfare effects evidence and the role of PM, specifically non-ecological effects on visibility, climate, and materials (Section 1.6). Lastly, Section 1.7, summarizes the causality determinations for all PM size fraction, exposure duration, and health and welfare effects combinations evaluated within this ISA.

[35] When discussing epidemiologic evidence, as detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{2.5}$ and $PM_{10-2.5}$ concentrations and a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ and $PM_{10-2.5}$ concentrations.

1.2 From Emissions Sources to Exposure to Particulate Matter

The characterization of human exposure is key to understanding the relationships between ambient PM (i.e., $PM_{2.5}$, $PM_{10-2.5}$, and UFP) and health effects. Exposure to PM is influenced by a variety of factors including, but not limited to, time-activity patterns, building characteristics, and amount of PM in the ambient air. The latter is influenced by sources and atmospheric processes contributing to ambient PM concentrations that together can influence the spatial and temporal patterns of PM. These patterns have implications for variation in exposure in the population, the adequacy of methods used to estimate exposure, and in turn, the strength of inferences that can be drawn about the health and welfare effects related to PM exposure.

1.2.1 Emission Sources and Distribution of Ambient Concentrations

PM is well defined as a complex mixture of solid and liquid droplets that is often characterized by distinct size fractions, i.e., $PM_{2.5}$, $PM_{10-2.5}$, and UFPs. The characteristics of each PM size fraction can vary in terms of: sources and emissions, atmospheric processes that result in PM formation, variability in concentrations over time and space, and monitoring.

Observations and new developments in the characterization of ambient PM build on the conclusions reported in the 2009 PM ISA, as summarized in CHAPTER 2. In the 2009 PM ISA, a decreasing trend in $PM_{2.5}$ concentrations were reported between 1999−2007, and a decreasing trend in PM_{10} concentrations between 1988−2007. In addition, for the years 2005−2007, there was considerable variability in daily average concentrations of $PM_{2.5}$. PM size was also observed to vary with location, with a generally larger fraction of PM_{10} mass accounted for by $PM_{10-2.5}$ size in western cities (e.g., Phoenix and Denver) and by $PM_{2.5}$ mass in eastern U.S. cities (e.g., Pittsburgh and Philadelphia). Compared to the larger PM size fractions, there was more limited information on the regional and temporal variability of UFPs. The composition of $PM_{2.5}$ nationally was also observed to vary, with higher sulfate concentrations in the summer and in the eastern U.S., and higher particulate organic carbon (OC) concentrations in the western and southeastern U.S. Little information was available on $PM_{10-2.5}$ or UFP composition. In urban areas, $PM_{2.5}$, PM_{10}, and UFPs were all observed to peak during morning rush hour and exhibited an evening rush hour peak that was broader than the morning peak and extended into the overnight period, reflecting the collapse of the mixing layer after sundown. In terms of measuring PM, notable advances had taken place in real-time PM mass measurement methods, single particle aerosol mass spectrometry methods, organic speciation methods, and dichotomous samplers for distinguishing $PM_{2.5}$ and $PM_{10-2.5}$. Major PM sources identified included combustion of fossil fuel, either by stationary sources or by transportation for primary PM, and formation of sulfates from SO_2 emitted mainly by electric power generating units (EGUs). Progress was also noted in understanding the chemistry of new particle formation and of secondary organic aerosol (SOA) formation. Background PM typically accounts for a

small fraction of urban $PM_{2.5}$ or PM_{10}, but high PM concentrations can occur during episodic events like wildfires or dust storms.

Changes in ambient PM characteristics as well as new research developments have occurred since the 2009 PM ISA. Ambient annual average $PM_{2.5}$ concentrations in the U.S. on average were 3.4 $\mu g/m^3$ lower in the period from 2013–2015 than in the period from 2005–2007 decreased from a 3-year average of 12 $\mu g/m^3$ for 2013–2015 to 8.6 $\mu g/m^3$ for 2005–2007, continuing the downward trend in national ambient $PM_{2.5}$ concentrations. However, while $PM_{2.5}$ concentrations were observed to decline, national average $PM_{10-2.5}$ concentrations were similar in both time periods. While monthly national average $PM_{2.5}$ concentrations were higher in summer than in winter from 2002–2008, this pattern is reversed from 2012–2015, when monthly average $PM_{2.5}$ concentrations became higher in winter than in summer. A greater reduction in sulfate concentrations than other component concentrations resulted in smaller sulfate contributions to $PM_{2.5}$ mass in 2013–2015 compared to 2005–2007, especially in the Eastern U.S. At many locations sulfate has been replaced by organic material as the greatest contributor to $PM_{2.5}$ mass. Much of the organic material is SOA, and there has been continued progress in understanding SOA precursors, formation processes, and components. The declines in $PM_{2.5}$ and sulfate concentrations are consistent with a large reduction in SO_2 emissions, mainly from decreased EGU coal combustion. Monitoring network changes have provided a more extensive set of observations for understanding the contributions of $PM_{2.5}$ and $PM_{10-2.5}$ to PM_{10}. The decrease in $PM_{2.5}$ concentrations has resulted in smaller $PM_{2.5}/PM_{10}$ ratios in many locations. PM_{10} in the East and Northwest is in the range of 50–60% $PM_{2.5}$, while PM_{10} in the Western U.S. is generally less than 50% $PM_{2.5}$. Routine measurement of UFPs is in its beginning stages, with only a few monitors beginning to report data.

1.2.1.1 Sources and Emissions of PM

PM is comprised of components that are directly emitted (primary particles) as well as formed through atmospheric chemical reactions involving gaseous precursors (secondary particles). The sources of PM vary with PM size fraction.

$PM_{2.5}$ can be generated from both natural and anthropogenic sources., The greatest contributors to primary $PM_{2.5}$ at the national level are agricultural dust, dust resuspended through on-road activities, and fires (i.e., wildfires, prescribed fires, and agricultural fires; see Section 2.3.1.1: and Figure 2-2). On a national scale, anthropogenic emissions have been estimated to account for 40% of total primary $PM_{2.5}$ emissions and 16% of total PM_{10} emissions (U.S. EPA, 2017). However, this does not account for secondary PM, most of which is derived from anthropogenic precursors. On an urban scale, sources that emit $PM_{2.5}$ vary from city-to-city. Generally, anthropogenic sources account for nearly all urban primary $PM_{2.5}$ emissions, and they include some combination of industrial activities, motor vehicles, cooking, and fuel combustion, and often wood smoke as well as construction and road dust. (Section 2.3.1.2). These

urban anthropogenic primary sources and more regional secondary generation both contribute substantially to $PM_{2.5}$ mass in urban locations.

Source contributions to primary $PM_{2.5}$ emissions have changed over time. For example, changes in both gasoline and diesel emissions controls have led to reductions in primary $PM_{2.5}$ emitted from newer vehicles, and primary emissions from stationary fuel combustion, industrial activities, and nonroad vehicles have also decreased (Section 2.3.1.2). Natural and international sources are generally minor contributors to $PM_{2.5}$ in urban areas. In many locations secondary PM accounts for the majority of $PM_{2.5}$ mass. The major PM precursors that can ultimately contribute to $PM_{2.5}$ mass include sulfur dioxide (SO_2), oxides of nitrogen (NO_X), ammonia (NH_3), and volatile organic compounds (VOCs) (Section 2.3.2.1). SO_2 emissions are mainly from electricity generating units (EGUs, 67%) while NO_X is emitted by several combustion sources, including on-road vehicles (34%), off-road vehicles (21%), and EGUs (13%). NH_3 emissions are dominated by livestock waste (55%) and fertilizer application (26%), and VOCs, on a national scale, mainly biogenic in origin (70%) (Section 2.3.2.1). Emissions of some $PM_{2.5}$ precursors, and subsequently their overall contribution to $PM_{2.5}$ mass, have changed over time (Section 2.3.2.1). Since the 2009 PM ISA, SO_2 emissions have been reduced from 13.9 million metric tons (MMT) in 2006 to 4.8 MMT in 2014, representing a 65% reduction and the greatest reduction among all precursor emissions (Section 2.3.2.1). NO_X emissions were also substantially reduced during the same time, decreasing from 19.4 MMT in 2006 to 13.5 MMT in 2014, representing an overall reduction of 30%. NH_3 emissions, however, have remained relatively constant over time, with estimates of 3.8 MMT in 2006 and 3.9 MMT in 2014 (Section 2.3.2.1).

While $PM_{2.5}$ is comprised of both primary PM, generated mostly from combustion-related activities, and secondary PM from atmospheric chemical reactions of precursor emissions, $PM_{10-2.5}$ is almost entirely primary in origin. $PM_{10-2.5}$ is produced by surface abrasion or by suspension of sea spray or biological material (e.g., microorganisms, pollen, plant and insect debris) (Section 2.3.3). Major sources on a national scale are unpaved road dust and agricultural dust, and in urban areas paved road dust and construction dust are usually major sources. Dust events can also result from international transport, and some of the dust particles in these events fall into the $PM_{10-2.5}$ size range. Primary biological aerosol particles can also be an important contributor to $PM_{10-2.5}$, including fungal spores, bacteria, viruses, and plant debris.

Ambient UFPs originate from two distinct processes, primary particles directly emitted from specific sources and new particle formation (NPF), which occurs because of particular atmospheric conditions that allow for particle nucleation (Section 2.3.4). UFP and $PM_{2.5}$ primary sources are largely indistinguishable because UFP is usually emitted by the same sources as $PM_{2.5}$, and grow out of the ultrafine size range through coagulation or gas-to-particle condensation over a short duration to form particles within the $PM_{2.5}$ size range. (Section 2.3.4.1). However, differences in the impact of various sources while particles are still mostly in the UFP size range can lead to differences in sources of greatest concern in both size ranges. For example, freshly emitted motor vehicle exhaust often occurs on busy

urban streets in residential neighborhoods, while emissions from electric power generation occur further away from human activity, and particles are likely to grow out of the UFP size range to a greater extent before reaching populated areas. It typically takes between about half a day and three days before newly-formed particles grow larger than 100 nm in diameter. As a result, although UFP size increases from 10 nm to 25 nm within 100 m, vehicle-related PM components are still mainly in the UFP size range as far as 1 km from a major highway.

Although relatively limited information is available on a source-by-source basis to capture changes in UFP emissions over time, analyses of individual sources where new source requirements have been instituted allow for an assessment of source contributions to UFP emissions. Most new research on UFP emissions has been focused on automobile exhaust, in part because of some of the highest observed UFP concentrations have been observed in near-road environments. For example, new requirements on heavy-duty diesel highway engines that were phased in from 2007–2010 and focused on reducing PM and NO_X emissions have led to reductions in UFP number concentration (NC) of more than 90% compared to earlier diesel engine models (Section 2.3.4.1). Although these newer diesel highway engines generate, on average, a smaller amount of UFP emissions compared to earlier models, there can still be discrete periods of extremely high UFP formation. This is due to thermal desorption of adsorbed sulfates that build up within the exhaust catalyst system and then can be released in a single burst (Section 2.3.4.1). Motor vehicles are a leading source of UFP emissions especially near roadways and recently similar observations of high UFP levels downwind of airports have also been reported. However, stationary point sources are also important, particularly at further distances from roadways. Gasoline and diesel-powered highway vehicles, nonroad diesel engines, and industrial sources are likely the largest sources of UFP in populated areas, where relative contributions of mobile and stationary sources of UFP are likely to vary considerably depending on location, season, and time of day.

1.2.1.2 Atmospheric Processes and PM Formation

The atmospheric processes that result in PM formation, specifically oxidation reactions to form ammonium sulfate and ammonium nitrate, have been well characterized in previous assessments (U.S. EPA, 2009, 2004) (Section 2.3.2.2). As a result, recent research has focused primarily on the formation of SOA, and has shown that SOA is a sizeable contributor to $PM_{2.5}$ mass under a variety of atmospheric conditions (Section 2.3.2.3). New research has increased our understanding of how a substantial amount of SOA is produced by several important processes: reactions of the biogenic VOC isoprene; cloud processing; and further oxidation of gas phase products formed from atmospheric VOC oxidation. Additionally, PM formation from biogenic VOC reactions has been reported to be enhanced by anthropogenic influences, including NO_X and SO_2 precursor emissions. (Section 2.3.2.3). Compositional analyses have shown that organosulfates and organonitrates often account for a large fraction of SOA, up to 5–10% for organosulfates and up to 10–20% for organic nitrates (Section 2.3.2.3). Examination of atmospheric processes that lead to SOA formation has led to observations that atmospheric aging

(oxidation) of organic aerosols increases reactive oxygen species activity of ambient PM (Section 2.5.1.1.7). Reactive oxygen species (ROS) have been shown to contribute to cellular oxidative stress in respiratory tract cells (Section 5.1.1).

In addition to exploring SOA formation, recent studies have further examined particle nucleation. New instrumentation has made it possible to measure atmospheric molecular clusters and to directly observe the process of particle nucleation (Section 2.3.4). This research has also focused on identifying the chemical species important in the particle nucleation process. Previous research had focused mainly on the role of sulfate and water, with increasing evidence that organic species were also involved. More recent research identified the importance of additional species, including ammonia and amines as well as extremely low volatility organic compounds in particle nucleation. (Section 2.3.4.2).

1.2.1.3 Monitoring and Modeling of PM

Broadly, PM is measured through the following: well-established long-term national monitoring networks based on well-established monitoring methods; individual monitors established for a specific period for the purposes of characterizing air quality or conducting an epidemiologic study using a variety of established or experimental methods; and satellite measurements. Depending on the PM size fraction, the extent to which information is available on ambient concentrations will vary as a direct result of the monitoring capabilities currently available.

For $PM_{2.5}$ and PM_{10}, extensive national air monitoring networks have been established based on Federal Reference Methods (FRMs) for supporting air quality analyses for the purposes of monitoring for compliance with the PM NAAQS, measurement of spatial and temporal trends of air pollutants, and to support research to assess exposure and health risks from PM exposures (Section 2.4.6). Because PM itself is a complex mixture, additional monitoring networks have been established to capture information on $PM_{2.5}$ components. Specifically, the Chemical Speciation Network (CSN), and the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, which was established for the specific purpose of understanding the relationship between PM composition and atmospheric visibility impairment, both monitor $PM_{2.5}$ components (Section 2.4.6).

Two new national monitoring networks provided additional monitoring of $PM_{2.5}$ and/or $PM_{10-2.5}$ (Section 2.4.6). The first national monitoring network was established as a result of the 2010 NO_2 NAAQS. This network instituted near-road monitors that were placed within 50 m of heavily trafficked roads in urban areas, and many of these near-road monitoring sites also conducted routine monitoring of $PM_{2.5}$. The NCore monitoring network was deployed starting in January 2011 and included measurements for $PM_{2.5}$ and $PM_{10-2.5}$. The $PM_{10-2.5}$ measurements were based on improved monitoring methods specified for $PM_{10-2.5}$ measurement methods to qualify as FRMs and Federal Equivalence Methods (FEMs), and compared to previously used methods that relied on taking the difference between PM_{10} and $PM_{2.5}$ FRM measurements (Section 2.4.6). The new $PM_{10-2.5}$ monitoring requirements are met by using

identical instrumentation for both $PM_{2.5}$ and PM_{10} except for the sampler cut-point; i.e., using the same sampler design, filter type, and filter face velocity for both $PM_{2.5}$ and $PM_{10-2.5}$ in the same sampler.

To date, most monitoring efforts with respect to PM focus on mass-based measurements of $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$. Recently, some monitors have been deployed to measure UFP concentrations. Routine network particle number concentration (NC) measurements were initiated at a few sites, mostly in New York state, which were made possible by the recent development of water-based condensation particle counters (CPCs) (Section 2.4.6). In other research, new CPCs have been developed, which are capable of measuring NC of particles with aerodynamic diameter 0.001 μm and larger, and these are especially useful for investigating the atmospheric nucleation of particles. (Section 2.4.3.1). Analysis of particle number count data from field studies shows that UFPs are likely to vary considerably among widely used methods, reflecting differences in the size ranges measured. While size ranges of ambient UFP measurements can vary depending on the monitor used, it is important to note that the ambient UFP size range varies from that used in experimental (i.e., animal toxicological and controlled human exposure) studies that rely on concentrated ambient particle (CAP) UFP exposures. Specifically, UFP CAPs result in particle size ranges up to 0.18−0.3 μm, which is larger than the nominal UFP size limit of less than 0.1 μm, which has previously been defined as the upper size cut as detailed in the 2009 PM ISA. Because the contribution to mass from particles less than 0.1 μm is relatively small, much of the mass may be associated with particles greater than 0.1 μm. However, as described in Section 2.4.3.1, the difference in particle number measurements between PM delivered with usual methods in controlled exposure studies and ambient UFP from which it originates is likely to be much less than the difference in mass (Section 2.4.3.3).

Some of the biggest developments since the 2009 PM ISA include the use of satellite-based measurements to estimate $PM_{2.5}$ concentrations and the continued evolution of chemical transport models (CTMs). Satellite-based measurements have become widely used and combined with modeled data and ground level measurements to extend spatial coverage and improve spatial resolution of $PM_{2.5}$ estimates (Section 2.4.5). Although satellite based $PM_{2.5}$ measurements allow for an expansion of the spatial coverage of epidemiologic studies, they are subject to measurement errors not encountered with FRM or other ground-based measurements, particularly due to data availability because of the inability to provide measurements during days with cloud or snow cover. This is because $PM_{2.5}$ is not directly measured and its estimation is based on computational algorithms involving a range of assumptions, such as vertical distribution and particle composition (Section 2.4.5). With respect to CTMs, advances have included the addition of biogenic VOC chemistry, organic aerosol aging, cloud chemistry, dry deposition, meteorological processes, wind-blown dust, and ammonia emissions. Collectively, these additions have resulted in demonstrable improvements in the prediction of seasonal variation and long-term changes in $PM_{2.5}$ concentrations (Section 2.4.7).

1.2.1.4 National PM Concentrations

Recent assessments of ambient PM concentrations have shown a general decline over time. $PM_{2.5}$ concentrations are generally lower than those reported in the 2009 PM ISA, decreasing from a national 3-year average of 12 $\mu g/m^3$ for 2005–2007 to 8.6 $\mu g/m^3$ for 2013–2015 (Section 2.5.1.1.1 and Section 2.5.2.1.1). Similar to the trend in $PM_{2.5}$ concentrations, national 3-year average PM_{10} concentrations have declined by 15% compared to those reported for 2005–2007, and are estimated at 21.1 $\mu g/m^3$ for 2013–2015, at least in part reflecting decreases in $PM_{2.5}$ concentrations. As detailed in Section 1.2.1.3, limited data are available from national monitors for $PM_{10-2.5}$ and UFP. As a result, it is difficult to assess trends in UFP and $PM_{10-2.5}$ concentrations over time (Section 2.5.1.1.5 and Section 2.5.2.1.3).

An examination of $PM_{2.5}$ composition trends further informs the overall reductions in $PM_{2.5}$ concentrations that have occurred over time. The biggest change in $PM_{2.5}$ composition that has occurred since the 2009 PM ISA, is the reduction in sulfate concentrations. Between 2000 and 2015 nationwide annual average sulfate concentration decreased by 17% at urban sites and 20% at rural sites. This change in sulfate concentrations is most evident in the eastern U.S., and has resulted in organic matter or nitrate now being the greatest contributor to $PM_{2.5}$ mass in most locations (Section 2.5.1.1.6). The observed decline in $PM_{2.5}$ sulfate concentrations can be attributed to a similar decline in SO_2 emissions. The overall reduction in sulfate concentrations likely contributed substantially to the decrease in national average $PM_{2.5}$ concentrations as well as the decline in the fraction of PM_{10} accounted for by $PM_{2.5}$, when compared to the years 2005–2007 (Section 2.5.1.1.6).

1.2.1.5 Spatial and Temporal Variability in PM Concentrations

Although there has been an overall reduction in national PM concentrations over time, there are distinct spatial and temporal patterns in PM concentrations. At a macro scale, $PM_{2.5}$ concentrations are generally higher and more spatially uniform in the eastern U.S. than in the western U.S. (Section 2.5.1.1.1). While $PM_{2.5}$ concentrations are generally higher in the eastern U.S., the highest reported concentrations are an exception to this trend, occurring in California. Especially high $PM_{2.5}$ concentrations are observed in the San Joaquin Valley, where multiple monitors recorded 3-year average concentrations greater than 14 $\mu g/m^3$, and in the Los Angeles basin, where 3-year average concentrations exceeded 12 $\mu g/m^3$ at several monitors. In the Eastern U.S., the highest $PM_{2.5}$ concentrations are in or near the Ohio Valley, extending eastward into Pennsylvania, where 3-year average concentrations for numerous monitors exceeded 10 $\mu g/m^3$. On a national scale there are distinct east and west patterns in long-term average $PM_{2.5}$ concentrations, but on an urban scale there is not a clear pattern of $PM_{2.5}$ spatial variability with some observations indicating relatively uniform concentrations while others depict a high degree of variability (Section 2.5.1.2.1).

Seasonal analyses have shown a change in the season with the highest $PM_{2.5}$ concentrations. Compared to the 2009 PM ISA, where the examination of seasonal $PM_{2.5}$ concentrations depicted higher concentrations in the summer, recent data indicate higher average $PM_{2.5}$ concentrations in the winter, which reflects lower SO_2 emissions and subsequently sulfate concentrations in the summer (Section 2.5.1.1.1 and Section 2.5.2.2.1). Within most urban areas, $PM_{2.5}$ exhibit a rush hour peak in the morning and evening (Section 2.5.2.3).

In general, the fraction of PM_{10} accounted for by $PM_{2.5}$ is higher in the eastern U.S. than in the western U.S. (Section 2.5.1.1.4). Compared to $PM_{2.5}$, $PM_{10-2.5}$ concentrations are more spatially variable (Section 2.5.1.2.3). Ninety-eighth percentile $PM_{10-2.5}$ concentrations greater than 40 $\mu g/m^3$ were observed in multiple locations in California, as well as in the southwestern states of Nevada, Arizona, New Mexico, Texas, and the central plains states of Oklahoma, Missouri, and Iowa, and the urban areas of St. Louis, MO, Cleveland, OH, and south Florida. While not directly comparable, PM_{10} concentrations, monitoring data for which are available for many more years, can inform, and are often consistent with, the observed spatial and temporal pattern of $PM_{10-2.5}$ concentrations. Compared to the 2004 AQCD (U.S. EPA, 2004), more PM_{10} in the eastern U.S. is now accounted for by $PM_{10-2.5}$ than before based on examining the fraction of PM_{10} comprised of $PM_{2.5}$. The $PM_{2.5}$ fraction of PM_{10} appears to have decreased from about 60–70% in –the 2004 PM AQCD to about 50–60% in 2013–2015 reported in this document, although the 2013–2015 observations are based on national network data and the 2004 data are based on a limited number of field study samples (Section 2.5.1.1.4). All U.S. regions display clear seasonal variations in $PM_{10-2.5}$ concentrations, with the lowest concentrations occurring around January and the highest occurring in the summer months (Section 2.5.2.2.2). Most $PM_{10-2.5}$ measurements have been based on 24-hour monitoring, however, considerably higher $PM_{10-2.5}$ concentrations have been observed using monitors capable of recording higher time resolution measurements, potentially indicating a tendency for intense $PM_{10-2.5}$ short-term episodes not captured by 24-hour monitoring (Section 2.5.1.1.3).

Data on the spatial and temporal variability in UFP concentrations is rather limited, particularly in the U.S. However, a single U.S. study that measured a full year of urban size-resolved particle number count measurements indicated about 90% of particles were smaller than 0.1 μm. (Section 2.5.1.1.5). The limited amount of available UFP measurements data indicated that the highest UFP concentrations occur in the winter and near roads with heavy traffic, often over short time periods (Section 2.5.1.2.4 and Section 2.5.2.2.3). Overall, UFP concentrations are more spatially variable than $PM_{2.5}$ (Section 2.5.1.2.4). Examinations of temporal variability show that UFP concentrations typically rise substantially in the morning and remain high into the evening hours when they reach their maximum, with distinct rush hour and early afternoon peaks. Additionally, there is evidence of seasonal impacts on the temporal variability of UFP concentrations, with high afternoon concentrations during warmer months possibly due to photochemical formation, and lower concentrations through the night (Section 2.5.1.1.5 and Section 2.5.2.2.3).

A detailed evaluation of the composition of $PM_{2.5}$, $PM_{10-2.5}$, and UFPs finds that each size fraction is dominated by a few components. For $PM_{2.5}$, there are clear geographic differences in its composition. In the eastern U.S., sulfate and organic matter are the highest contributors to total mass while in the western U.S. organic matter most often is the highest contributor, although sulfate, nitrate, and crustal material can also be abundant (Section 2.5.1.1.6). When examining the absolute concentrations of specific components, the highest nitrate concentrations are observed in the western U.S., particularly in California, but with some elevated concentrations in the upper Midwest. Seasonally, nitrate concentrations are much higher in the winter than summer in all locations (Section 2.5.1.1.6). Organic and elemental carbon concentrations are both more uniformly distributed in the eastern U.S., but more variable among western U.S. locations. The highest urban concentrations in the western U.S. occur during fall and winter (Section 2.5.1.1.6). Crustal material is a substantial contributor to $PM_{2.5}$ mass in dry areas of the western U.S., such as in Phoenix and Denver (Section 2.5.1.1.6). For $PM_{10-2.5}$, as noted previously concentrations are highest in southwestern U.S. and are observed to be largely dominated by crustal material, but organic material can also represent a substantial contribution to mass, as well as biological material like bacteria, viruses, fungal spores, pollen, and plant debris (Section 2.5.1.1.6). For UFPs there is still relatively limited information on its composition, but initial data indicate that urban UFPs are rich in organic and elemental carbon, while sulfate and ammonium are likely to be substantial contributors to UFPs in areas where new particle formation occurs (Section 2.5.1.1.6).

Background PM generally refers to PM that is formed by sources or processes that cannot be influenced by actions to control PM concentrations. Various background definitions have been used for NAAQS reviews. U.S. background concentration of a pollutant is the concentration resulting from natural primary and precursor sources everywhere in the world plus anthropogenic sources outside of the U.S., Canada, and Mexico. Similarly, North American background concentrations is the concentration resulting from natural primary and precursor sources everywhere in the world plus anthropogenic sources outside of the U.S., Canada, and Mexico. U.S. background sources of PM include wind erosion of natural surfaces, volcanic production, wildfires, sea salt, biological material like pollen and spores, SOA produced by oxidation of biogenic hydrocarbons, and international transport. Background PM can be episodic, as in the case of volcanic eruptions, forest fires, and dust storms or more consistent, as in the case of a relatively constant, low level contributions from natural and intercontinental sources outside of major events. Nationally, it has been estimated that wildfire smoke contributes between 10% and 20% of primary $PM_{2.5}$ emissions per year, and intercontinental transport contributes 0.05 to 0.15 $\mu g/m^3$ to annual average $PM_{2.5}$ concentrations in the U.S., but that this contribution varies by region and season. On average, natural sources including soil dust and sea salt have been estimated to account for approximately 10% of U.S. urban $PM_{2.5}$ (Section 2.5.4).

1.2.1.6 Summary

Since the 2009 PM ISA there are new developments and observations in the characterization of ambient PM. For $PM_{2.5}$, these include observations of a steep decline in SO_2 precursor concentrations, replacement of sulfate with organic matter as the greatest contributor to $PM_{2.5}$ mass in many locations in the eastern U.S., and a substantial decrease in national average $PM_{2.5}$ concentration. A large body of new research has also refined the overall understanding of SOA formation processes. Improvements in CTM methods have resulted in demonstrable improvements in the prediction of seasonal variation and long-term changes in $PM_{2.5}$. Extensive new network monitoring for $PM_{10-2.5}$ has greatly increased the amount of data available for assessing relative amounts of $PM_{2.5}$ and $PM_{10-2.5}$, showing that $PM_{10-2.5}$ as a fraction of PM_{10} has increased in the eastern U.S. as sulfate and $PM_{2.5}$ have decreased, and that in many western locations the contribution of $PM_{10-2.5}$ to PM_{10} exceeds the contribution of $PM_{2.5}$ to PM_{10}. This new monitoring effort has further informed the understanding of seasonal and regional differences in $PM_{10-2.5}$ concentrations. Recent studies focusing on UFPs, largely supports observations in the 2009 PM ISA, but new areas of emphasis include instrumentation for measuring particles as small as 1 nm and the initiation of long-term monitoring in a few U.S. locations, which will facilitate future research. However, network data are still sparse, and there is still far less information regarding patterns of spatial and temporal variability of UFP in comparison to $PM_{2.5}$ or $PM_{10-2.5}$. Differences in monitoring methods and the lack of a consistent definition also make comparison of UFP data difficult between different field studies or methods.

1.2.2 Assessment of Human Exposure

Findings from the recent exposure assessment literature build on evidence presented in the 2009 PM ISA for the assessment of PM exposures. The 2009 PM ISA found that spatial variability of $PM_{10-2.5}$ and UFP at micro-to-neighborhood scales was greater than that of $PM_{2.5}$, and primary $PM_{2.5}$ components, such as EC, exhibited greater spatial variability than $PM_{2.5}$ components produced through atmospheric chemical reactions, such as NO_3^- or SO_4^{2-}. Regional variability in PM composition was also noted and thought to result from differences among sources in different parts of the country. Models, such as land use regression (LUR), were discussed as tools intended to characterize spatially variable components or size fractions, but limitations in the LUR's ability to adequately capture spatial variability were identified in several papers reviewed. Additionally, variability in the PM size distribution, PM composition, and infiltration was identified across regions as factors that could influence individual exposure to PM. Unmeasured variability in ambient PM concentration, size fractions, and composition were noted to cause potential uncertainty in estimates of exposure concentrations and health effect estimates. The recent literature advances the state of exposure science by presenting innovative methodologies to estimate PM exposure, detailing new and existing measurement and modeling methods, and further informing the influence of exposure measurement error due to new and existing exposure concentration estimation methods on associations between PM and health effects reported in the epidemiologic study literature.

New evidence supports older findings that appropriate surrogates for exposure concentration may depend on PM size distribution, because spatial variability in PM concentrations varies with particle size (Section 3.4.3.2). Multiple techniques have recently been developed or improved to assign PM exposure concentrations in epidemiologic studies. These methods include personal monitors, data averaging across monitors, interpolation methods, LUR models, spatiotemporal models, CTMs, dispersion models, microenvironmental models, and satellites (Section 3.3). Fixed-site monitors also continue to be used frequently to estimate exposure concentration. Each method has strengths and limitations. Accordingly, errors and uncertainties in the exposure assessment methods can add bias and uncertainty to health effect estimates from epidemiologic studies on the health effects of PM exposure.

Ambient PM data from individual sites continue to be used widely in health studies as a surrogate for PM exposure concentration, because fixed-site monitors provide a continuous record of ambient PM concentrations over many years (Section 3.3.1.1). For $PM_{2.5}$, the concentration profile tends to be more homogeneous across the urban or neighborhood scale, ambient concentrations estimated at fixed-site monitors may reflect exposure concentrations. However, the higher degree of spatial variability in ambient $PM_{10-2.5}$ and UFP across an urban area may not be captured by a fixed-site monitor. As a result, uncharacterized variability in a time-series of exposure concentrations across space, resulting from use of fixed-site monitoring data, in a time-series epidemiologic study of $PM_{10-2.5}$ or UFP exposure may tend to attenuate health effect estimates (Section 3.4.5.1). For long-term exposure studies, bias may occur in either direction depending on whether the fixed-site monitor is over- or underestimating ambient $PM_{10-2.5}$ or UFP exposure concentration for the population of interest (Section 3.4.5.2). In all study types, use of fixed-site monitoring ambient $PM_{10-2.5}$ or UFP concentrations in lieu of the true exposure is expected to widen confidence intervals beyond what would be obtained if the true exposure were used. Personal monitors directly measure PM exposure, but they produce a relatively limited data set, making them most suitable for panel epidemiologic studies (Section 3.4.5.1.2). Without accompanying geographic positioning system (GPS) or time-activity diary data, it is impossible to distinguish ambient PM exposure from exposure to PM of nonambient origin in these studies.

Models of PM concentration can be used to develop exposure surrogates for individuals and large populations when personal exposure measurements are unavailable (Section 3.3.2). Recent developments have been made to advance techniques for spatiotemporal modeling, which typically combine universal kriging with variables describing land use, population characteristics, emissions, and geographic features (Section 3.3.2.3). GIS-based spatiotemporal models of concentration that are used as exposure surrogates have produced out-of-sample cross-validation (i.e., out-of-sample $R^2 > 0.8$) for $PM_{2.5}$ and its components, some of which have more spatially varying concentration fields than $PM_{2.5}$ mass concentration. Overly-smoothed exposure concentration surfaces from spatiotemporal models have been shown to bias the health effect estimate towards the null (i.e., underestimating the true health effect) with decreased probability that the confidence intervals contain the true health effect, particularly when the actual spatial variability is much higher than what is represented by the model (Section 3.4.5.2). Bias correction and bootstrap calculation of standard errors have been shown to improve health effect estimate prediction

from spatiotemporal models when the exposure estimates have a classical-like error structure. A study of $PM_{2.5}$ mass and components, including EC, OC, Si, and S, where the exposure model errors had a Berkson structure, did not exhibit improvement of the health effect estimate when bootstrap simulation of the standard error was applied. When the exposure estimates have a Berkson-like error structure, health effect estimate predictions would only be expected to improve when model covariates are chosen so that the statistical distribution of the modeled exposure concentrations is close to the distribution of the true exposure concentrations.

Recent developments have been made for mechanistic models, such as dispersion models and CTMs, to simulate the transport, dispersion, and (in the case of CTMs) atmospheric chemistry of ambient PM (Section 3.3.2.4). Hybrid approaches to combine exposure concentration predictions from CTMs with those from fixed-site monitoring data or dispersion models have grown since the 2009 PM ISA. CTMs are limited in their spatial resolution, which is typically at length scales of 4 km or 12 km (and sometimes down to 1 km). Data fusion techniques merge CTMs with dispersion model results or fixed-site monitoring data. They are designed to estimate spatial variability of exposure concentrations at the subgrid scale, typically through a hierarchical modeling framework. These models have good cross-validation and have the potential to reduce exposure measurement error and resulting bias and uncertainty in health effect estimates produced by epidemiologic models of long-term exposure to PM, even for spatially-varying size fractions and components.

Several advancements to data fusion techniques have been made since the 2009 PM ISA to merge aerosol optical density (AOD) observations from satellite images with surface-level PM measurements from fixed-site monitors (Section 3.3.3). Regression models have been developed to calibrate the AOD observations to surface measurements of $PM_{2.5}$, and $PM_{2.5}$ exposure concentrations have then been estimated from those models in locations where surface measurements are unavailable. Land use or other geographical variables incorporated in these models have been shown to improve cross-validation and reduce error in estimates of exposure concentrations, and increasing the number of monitors used to fit the model has reduced bias and uncertainty in the exposure estimates. Hence, hybrid modeling approaches combining satellite data with fixed-site monitoring data and LUR or spatiotemporal modeling results have the potential to reduce bias and uncertainty in health effect estimates reported in epidemiologic studies of short- and long-term exposure to $PM_{2.5}$. Satellite data techniques have not typically been applied to model spatially-variable UFP, $PM_{10-2.5}$, or $PM_{2.5}$ component exposure concentration fields. Epidemiologic studies where PM exposure concentration is derived from a hybrid satellite-LUR model have reported larger magnitude health effect estimates with increasing spatial resolution (i.e., dividing the spatial domain into many smaller areas in which concentration is modeled) of the exposure concentration surfaces. If the effect estimate derived from the hybrid model was shown by cross-validation to be more accurate than a low-resolution model, then this finding suggests that low spatial resolution (i.e., a spatial domain with a small number of large areas in which concentration is modeled) of the PM exposure concentration surface may cause bias of the health effect estimate towards the null to underestimate the true health effect in a long-term exposure study (Section 3.4.5.2).

Among the methods evaluated, only personal monitoring and microenvironmental modeling account for indoor exposure to ambient PM (Section 3.3.1.2). Particles are deposited during the process of infiltration to indoor or vehicle microenvironments, to produce an infiltration factor (F_{inf}) <1 (Section 3.4.1.1). As described in the 2009 PM ISA, F_{inf} varies with season, window opening, building age, wind speed and particle size distribution (with F_{inf} lower for $PM_{10-2.5}$ compared with $PM_{2.5}$). Recent studies have reported lower F_{inf} for UFP compared with F_{inf} for $PM_{2.5}$, potentially reflecting diffusion-driven surface deposition losses for UFP during the infiltration process. In a study of the influence of exposure estimates on health effect estimates in a time-series epidemiologic study of PM exposure, use of a fixed-site monitor in lieu of a microenvironmental model that accounted for infiltration produced considerably attenuated health effect estimates (Section 3.4.5.1). Infiltration of PM through a building envelope may change the temporal variability of the indoor PM concentration time-series, resulting in reduced correlation between the health effect of interest and the estimated exposure concentration. In a study of the influence of modeled exposure concentrations on health effect estimates in an epidemiologic study of long-term average PM exposure, simulating indoor concentrations produced unbiased health effect estimates. Furthermore, the health effect estimate was biased towards the null with inflated confidence intervals after omitting a term for infiltration in a LUR or spatiotemporal model. Bias towards the null leads to underestimation of the true health effect (Section 3.4.5.2).

Exposure to copollutants may result in some confounding of the PM health effect estimate if exposure to the copollutants and their relationships to the health effect of interest are both correlated with PM exposure (Section 3.4.3). Median correlations of 24-hour ambient $PM_{2.5}$ with concentrations of some ambient gases (CO, NO_2, O_3) from the U.S. EPA Air Quality System (AQS) during 2013−2015 were as high as Pearson $R = 0.5$, although correlation varied with season (highest for O_3 in summer and for CO and NO_2 in winter). The upper end of the distribution of correlations approached one for these gases. Copollutant correlation data for short-term concentration measurements from the literature since the 2009 PM ISA were consistent with the AQS data. For $PM_{10-2.5}$, median correlations of 24-hour ambient concentrations during the same time period were as high as Pearson $R = 0.4$ but with upper correlations typically below Pearson $R = 0.7$−0.8. Median correlations between $PM_{2.5}$ and $PM_{10-2.5}$ range between 0.2 and 0.5, with higher values in summer and fall. Data for UFP correlations were very limited, but they indicate correlations as high as Pearson $R = 0.5$ for NO_2 and NO_X. Sites with moderate-to-strong correlations ($R > 0.4$) may introduce a greater degree of confounding into epidemiologic results, depending on the relationship between the copollutants and the health effect of interest.

Some epidemiologic studies of the health effects of PM exposure have examined potential associations between health effects and exposure to PM components (Section 3.4.4) since the 2009 PM ISA. An examination of the composition of $PM_{2.5}$ using data from AQS found that the highest Pearson correlations between $PM_{2.5}$ mass and $PM_{2.5}$ component concentrations occurred for OC, SO_4^{2-}, EC, and NO_3^-. A large percentage of $PM_{2.5}$ mass concentration is a product of atmospheric chemistry. The recent peer-reviewed literature showed high correlations of $PM_{2.5}$ mass concentrations with concentrations of secondary SO_4^{2-} and NO_3^- as well as primary V and Zn. Similarly, high correlations between the

quasi-ultrafine $PM_{0.25}$ and V were observed in recent studies for $PM_{0.25}$ exposure concentrations, and correlations near Pearson $R = 1$ during the winter support the notion that heating oil combustion plays a role in these associations. For $PM_{10-2.5}$, the largest correlation was for Si, possibly in dust. Median correlations reported from AQS and the literature for $PM_{10-2.5}$ with all other $PM_{10-2.5}$ components were Pearson $R < 0.5$, indicating that $PM_{10-2.5}$ is not strongly associated with combustion. Generally, $PM_{2.5}$ components reflect the secondary nature of their production, the $PM_{0.25}$ components reflect combustion, and $PM_{10-2.5}$ components reflect mechanical generation.

In summary, exposure error tends to produce underestimation of health effects in epidemiologic studies of PM exposure, although bias in either direction can occur. There are new developments in assessment of PM exposure, including hybrid spatiotemporal models that incorporate satellite observations of AOD, land use variables, surface monitoring data from FRMs, and/or CTMs. Improvements in spatial resolution of the $PM_{2.5}$ concentration surface have reduced bias and uncertainty in health effects estimates. However, high correlations with some gaseous copollutants necessitate evaluation of the impact of confounding on health effects estimates, using two-pollutant models to ascertain robustness of epidemiologic study results. $PM_{10-2.5}$ and UFP concentrations tend to be more spatially variable than $PM_{2.5}$ concentrations, and data are either unavailable or less often available to fit or validate hybrid models for those size fractions. As a result, there is typically less uncertainty in health effect estimates derived from both monitored and modeled exposure estimates for $PM_{2.5}$ compared with $PM_{10-2.5}$ and UFP.

1.3 Dosimetry of PM

Particle dosimetry refers to the characterization of deposition, translocation, clearance, and retention of particles and their components within the respiratory tract and extra-pulmonary tissues. The dose from inhaled particles deposited and retained in the respiratory tract is governed by several factors. These factors include exposure concentration and duration, activity and breathing conditions (e.g., nasal vs. oronasal route and minute ventilation), and particle properties (e.g., particle size, hygroscopicity, and solubility in airway fluids and cellular components). Basic information related to the mechanisms of particle deposition and clearance and the influence of disease severity on these mechanisms has not changed over the last several PM NAAQS reviews. Compared to prior reviews, species similarities and differences in the amounts of inhaled PM reaching the lower respiratory tract is now better understood and quantified. Additionally, some older literature on route of breathing in humans, that was not included in prior reviews, has come to light and shows differences in route of breathing as a function of age and sex. New data on particle translocation across the olfactory mucosa into the brain and from the alveolar epithelium into the blood also now allows for improved estimates of the importance of these processes in humans.

To be deposited in the respiratory tract, particles need to first be inhaled. Inhalability refers to the fraction of particles that can enter the upper respiratory tract (i.e., the head) during inhalation and is dependent on the aerodynamic diameter of the particle (d_{ae}). A commonly used occupational criterion of particle inhalability in humans based on the d_{ae} of particles, predicts that as d_{ae} increases from 1−10 μm, inhalability decreases from ~97 to ~77%, plateauing at 50% for particles ~40 μm in diameter (Section 4.1.5). The occupational criterion is for relatively high wind speeds (>1 m/s). In calm air, inhalability decreases toward zero with increasing d_{ae} above about 20 μm for nasal and 30 μm for oral breathing. There is evidence for much lower particle inhalability in infants than adults. In rodents, inhalability decreases more rapidly than in humans, from 80 to 44%, as d_{ae} of particles increases from 2.5 to 10 μm especially for faster breathing rates. Inhalability and nasal deposition are particularly important considerations influencing how much PM makes it into the lower respiratory tract of rodents relative to humans (Section 4.1.6).

The route of breathing, breathing pattern (volume and rate), and particle size are among the factors affecting the amount of PM that enters the body and may subsequently deposit in the respiratory tract. With increasing physical activity, there is an increase in minute ventilation and a shift from nasal to oronasal breathing, and depending on the size fraction of PM inhaled, potentially greater PM penetration into the lower respiratory tract (i.e., the lungs). Even at rest, differences have been observed by age, sex, disease status, and body mass index in the fraction of oral versus nasal breathing (Section 4.1.3). Children inhale a larger fraction of air through their mouth than adults, and males tend inhale a larger fraction of air through their mouth than females (across all ages). Individuals with allergies or upper respiratory infections experience increased nasal resistance, and thus, an increased fraction of oral breathing. Obesity, especially in boys, may also contribute to increased nasal resistance and an increased oral fraction of breathing relative to normal weight children. Due to their increased amount of oral breathing, these individuals may be expected to have greater PM penetration into the lower respiratory tract than healthy, normal weight adults. Children may also be expected to have a greater intake dose of PM per body mass than adults. Route of breathing is instrumental in determining the amount of PM inhaled and also impacts the size of particles that can reach the lower respiratory tract. In humans, the fraction of a breath entering through the mouth increases the fraction of particles reaching the lower respiratory tract (Figure 4-3). In contrast, rodents are obligatory nasal breathers and only a small percentage of larger particles (i.e., >3 μm) reaches the lower respiratory tract (Figure 4-4).

Particle deposition in the respiratory tract occurs predominantly by diffusion, impaction, and sedimentation (Section 4.2). Total respiratory tract particle deposition can reach nearly 100% in humans for particles smaller than approximately 0.01 μm (via diffusion) and greater than 10 μm (via sedimentation and impaction), but is minimal for particles between 0.3 to 0.7 μm. The nose and mouth represent the first line of defense against particles depositing in the lower respiratory tract, with roughly 100% of particles 10 μm or greater depositing in the human nose. Inter-species differences in the inhalability and nasal deposition of particles has also been shown to affect the size of particles that can enter the respiratory tract and the percentage of particles deposited in various regions. While larger

particles tend to deposit in the nose in humans, in rodents almost 100% of particles >5 μm are deposited in the nose. Additionally, oronasal breathing in humans contributes to greater penetration of coarse particles into the lower respiratory tract, whereas rats breath only nasally. There are also differences between children and adults in terms of breathing patterns and ventilation, indicating that children may receive a higher dose per lung surface area of ambient PM in the lower respiratory tract. Respiratory disease can lead to differences in both total deposition and deposition patterns relative to the disease-free lung. In general, the PM dose rate is increased by lung disease, but depends on the severity of and type of disease.

For any given particle size, the pattern of poorly soluble particle deposition influences clearance by partitioning deposited material between regions of the respiratory tract (Section 4.3). While particles depositing in the mouth are generally swallowed or removed by expectoration, particles deposited in the posterior nasal passages or tracheobronchial (TB) airways are moved by mucociliary transport towards the nasopharynx and swallowed. In the alveolar region clearance occurs mainly via macrophage phagocytosis. Clearance is more rapid in rodents than humans and has been shown to decrease with age beyond adulthood. Human studies have shown that ultrafine carbon particles do not rapidly or significantly translocate from the lungs into the circulation (Section 4.3.3.2). However, a new human study has demonstrated some translocation of nano-sized gold particles from the lungs into circulation. The finding of material in the blood in this new human study, but not prior human studies may, in part, be a matter of an increased signal to noise afforded in this new methodology and/or an indication that there is a difference in particle translocation from the lung depending on the inhaled particle type. Animal studies using poorly soluble nano-sized gold and iridium (Ir) particles have provided more extensive evidence of translocation into blood and secondary organs. The estimated urinary elimination by 24 hours post-inhalation of the gold nanoparticles is nearly identical between humans and rats. Soluble materials deposited in the respiratory tract can enter the blood more rapidly than insoluble materials. Recent evidence across species indicates that particles of varying composition, particle size (less than 200 nm diameter), and solubility can also translocate to the brain via the olfactory bulb. It remains unclear, though, whether translocation to the olfactory bulb and brain regions varies by species and whether certain species are more predisposed to this translocation route.

There is a dosimetric basis for several particle sampling conventions used to quantify airborne PM concentrations. The U.S. EPA has size-selective sampling conventions for fine particles indicated by $PM_{2.5}$ and PM_{10} as an indicator for the purposes of regulating the thoracic coarse particles (i.e., the inhalable particles that remain if $PM_{2.5}$ particles are removed from a sample of PM_{10}; aka $PM_{10-2.5}$). $PM_{2.5}$ is not well representative [nor was it intended to be] of the occupational definition of respirable particles which has a 50% cut-point at 4 μm versus 2.5 μm for the $PM_{2.5}$ sampler (Figure 4-2). The selection of $PM_{2.5}$ for the NAAQS was mainly to delineate the atmospheric fine (combustion derived, aggregates, acid condensates, secondary aerosols) and coarse (crustal, soil-derived dusts) PM modes and for consistency with community epidemiologic health studies reporting various health effects associated with $PM_{2.5}$ but not on dosimetric considerations as was the case for the respirable particle sampler convention. Although

the respirable sampling convention has a dosimetric basis, it is reflective of the total PM mass concentration to which the alveolar region may be exposed not the PM mass deposition or dose. PM_{10} is often referred to as the thoracic fraction of inhalable particles and there is an occupational sampling convention for thoracic particles both of which have a 50% cut-point at about 10 μm (Figure 4-2). However, it should be recognized that the fraction of inhaled 10 μm particles reaching the thorax is <20% for most activity levels and breathing habits. Breathing completely through the mouth, fraction of inhaled 10 μm particles reaching the thorax approaches 40%. Thus, using a 50% cut-point at 10 μm provides a conservative (protective) overestimate of thoracic particles.

1.4 Evaluation of the Health Effects of PM

This ISA evaluates relationships between an array of health effects and short-term and long-term exposures to PM (i.e., $PM_{2.5}$, $PM_{10-2.5}$, and UFPs) in epidemiologic, controlled human exposure, and animal toxicological studies. In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. Short-term exposures are defined as those with durations of hours up to one month, with most studies examining effects related to exposures in the range of 24 hours to 1 week. Long-term exposures are defined as those with durations of more than 1 month to years. As detailed in the Preface , the evaluation of the health effects evidence focuses on exposures conducted at concentrations of PM that are relevant to the range of human exposures across ambient microenvironments (up to 2 mg/m^3, which is one to two orders of magnitude above ambient concentrations), and (1) include a composite measure of PM[36] or (2) apply some approach to assess the direct effect of a specific PM size-fraction when the exposure of interest is a source-based mixture (e.g., diesel exhaust, gasoline exhaust, wood smoke). Drawing from evidence related to the biological plausibility of PM-related health effects and the broader health effects evidence described in detail in Chapters 5−11, information on dosimetry in CHAPTER 4 and Section 1.4, as well as issues regarding exposure assessment and potential confounding described in CHAPTER 3 and Section 1.3, the subsequent sections and accompanying table (Table 1-2) summarize the key evidence that informed the causality determinations for relationships between PM exposure and health effects, specifically those relationships where a "*causal*" or "*likely to be causal*" relationship has been concluded (Table 1-1). Those relationships between PM and health effects where a "*suggestive of, but not sufficient to infer*" or "*inadequate*" causality determination has been concluded are noted in Table 1-7, but more fully discussed in the respective health effects chapters.

[36] Composite measures of PM may include mass, volume, surface area, or number concentration.

Table 1-1 "Causal" and "likely to be causal" causality determinations for short- and long-term PM exposure.

Size Fraction	Health Effects Category	Exposure Duration	Causality Determination	Section
$PM_{2.5}$	Respiratory	Short-term	Likely to be causal	1.4.1.1.1
		Long-term	Likely to be causal	1.4.1.1.2
	Cardiovascular	Short-term	Causal	1.4.1.2.1
		Long-term	Causal	1.4.1.2.2
	Nervous System	Long-term	Likely to be causal	1.4.1.3.1
	Cancer	Long-term	Likely to be causal	1.4.1.4.1
	Mortality	Short-term	Causal	1.4.1.5.1
		Long-term	Causal	1.4.1.5.2
UFP	Nervous System	Long-term	Likely to be causal	1.4.3.1

1.4.1 Health Effects of $PM_{2.5}$

Substantial scientific evidence exists across disciplines (i.e., animal toxicology, controlled human exposure, and epidemiology), with additional support from studies examining biological plausibility, showing that both short- and long-term $PM_{2.5}$ exposure can result in a range of health effects, from changes in circulating biomarkers to mortality. However, the overall confidence in the $PM_{2.5}$ exposure – health effects relationship varies depending on the exposure duration (i.e., short- or long-term) and broad health category (e.g., cardiovascular effects, respiratory effects) examined. Across the broad health effects categories examined, the evidence supporting biological plausibility varies, but generally includes modulation of the autonomic nervous system and inflammation as part of the pathways leading to overt health effects. Discussions of subsequent events that could occur due to deposition of inhaled $PM_{2.5}$ in the respiratory tract are detailed in the biological plausibility sections of each health chapter and summarized in the following sections when detailing the health effects evidence.

1.4.1.1 Respiratory Effects

Recent scientific evidence continues to support a "*likely to be causal relationship*" between both short- and long-term $PM_{2.5}$ exposure and respiratory effects, which is consistent with the conclusions of

the 2009 PM ISA. These causality determinations are based on the consistency of findings within disciplines, coherence among evidence from controlled human exposure, epidemiologic, and toxicological studies, and biological plausibility for respiratory effects, such as asthma exacerbation, development of asthma, COPD exacerbation, and respiratory mortality.

1.4.1.1.1 Respiratory Effects Associated with Short-Term $PM_{2.5}$ Exposure

Epidemiologic studies provide strong evidence for overt respiratory effects, including respiratory-related emergency department visits and hospital admissions and respiratory mortality due to short-term $PM_{2.5}$ exposure, but there is more limited evidence of respiratory effects from experimental studies to provide coherence. Collectively this evidence supports a "*likely to be causal relationship*" between short-term $PM_{2.5}$ exposure and respiratory effects, which is consistent with the conclusions of the 2009 PM ISA (Table 1-2). This conclusion is based on multiple recent epidemiologic studies demonstrating generally consistent, positive associations with emergency department visits for asthma and combined respiratory-related diseases, as well as with respiratory mortality. Evidence from animal toxicological studies, although limited, is supportive of and provides biological plausibility for the associations observed in the epidemiologic studies.

Recent epidemiologic studies continue to provide strong evidence for a relationship between short-term $PM_{2.5}$ exposure and several respiratory-related endpoints, including asthma exacerbation (Section 5.1.2.1), COPD exacerbation (Section 5.1.4.1), and combined respiratory-related diseases (Section 5.1.6), particularly from studies examining emergency department visits and hospital admissions. The consistent positive associations between short-term $PM_{2.5}$ exposure and asthma and COPD emergency department visits and hospital admissions are supported by epidemiologic studies demonstrating associations with other respiratory-related effects such as symptoms and medication use that are indicative of asthma and COPD exacerbations (Section 5.1.2.2 and Section 5.1.4.2). The collective body of epidemiologic evidence for asthma exacerbation is more consistent in children than in adults. Epidemiologic studies examining the relationship between short-term $PM_{2.5}$ exposure and respiratory mortality provide evidence of consistent positive associations, demonstrating a continuum of effects (Section 5.1.9).

Building off the studies evaluated in the 2009 PM ISA, recent epidemiologic studies expand the assessment of potential copollutant confounding. There is some evidence that $PM_{2.5}$ associations with asthma exacerbation, combined respiratory-related diseases, and respiratory mortality remain relatively unchanged in copollutant models with gaseous pollutants (i.e., O_3, NO_2, SO_2, with more limited evidence for CO) and other particle sizes (i.e., $PM_{10-2.5}$) (Section 5.1.10.1). The uncertainty related to whether there is an independent effect of $PM_{2.5}$ on respiratory health, is partially addressed by findings of animal toxicological studies. Specifically, short-term exposure to $PM_{2.5}$ enhanced asthma-related responses in an animal model of allergic airways disease and enhanced lung injury and inflammation in an animal model of COPD (Section 5.1.2.4.3 and Section 5.1.4.4.2). Although there is a broad body of experimental

evidence demonstrating respiratory effects due to short-term $PM_{2.5}$ exposure it is not entirely coherent with the results of epidemiologic studies. However, the experimental evidence does provide biological plausibility for some respiratory-related endpoints. This includes limited evidence of altered host defense and greater susceptibility to bacterial infection as well as consistent evidence of respiratory irritant effects. Animal toxicological evidence for other respiratory effects is inconsistent. Additionally, controlled human exposure studies conducted in people with asthma or COPD show minimal respiratory effects due to short-term $PM_{2.5}$ exposure, such as decrements in lung function and pulmonary inflammation.

1.4.1.1.2 Respiratory Effects Associated with Long-Term $PM_{2.5}$ Exposure

Epidemiologic studies provide strong evidence for effects on lung development, with additional evidence for the development of asthma in children due to long-term $PM_{2.5}$ exposure. Evidence from animal toxicological studies, although limited in number, supports the findings of these epidemiologic studies. There is also epidemiologic evidence for a decline in lung function in adults. Collectively this evidence supports a "*likely to be causal relationship*" between long-term $PM_{2.5}$ exposure and respiratory effects, which is consistent with the conclusions of the 2009 PM ISA (Table 1-2).

Recent epidemiologic studies continue to support an association between long-term $PM_{2.5}$ exposure and several respiratory-related endpoints in children and adults. In children, studies in multiple cohorts provide strong evidence for decrements in lung function growth (Section 5.2.2.1.1). Robust and persistent effects were observed across study locations, exposure assessment methods, and time periods. An animal toxicological study demonstrating impaired lung development resulting from pre- and post-natal $PM_{2.5}$ exposure provides biological plausibility for these findings (Section 5.2.2.1.2). Results of prospective cohort studies in children also provide some evidence for asthma development in children, and are supported by studies of asthma prevalence in children, childhood wheeze, and pulmonary inflammation (Section 5.2.3). Biological plausibility is provided by an animal toxicological study of long-term $PM_{2.5}$ exposure demonstrating the development of an allergic phenotype and increase in airway responsiveness (Section 5.2.3.3.2). There is limited evidence of increased bronchitic symptoms and hospitalization in children with asthma in relation to long-term $PM_{2.5}$ exposure (Section 5.2.7). In adults, long-term $PM_{2.5}$ exposure was associated with an acceleration of lung function decline (Section 5.2.2.2.2). Consistent evidence was observed for respiratory mortality and cause-specific respiratory mortality for COPD and infection (Section 5.2.10), providing evidence of a continuum of effects in response to long-term $PM_{2.5}$ exposure.

Although still limited in number, recent epidemiologic studies further examine potential copollutant confounding. There is some evidence that $PM_{2.5}$ associations with respiratory mortality remained robust in models with some gaseous pollutants (Section 5.2.10); however, there is limited assessment of potential copollutant confounding when examining respiratory morbidity outcomes. The uncertainty related to the independence of $PM_{2.5}$ effects is partially addressed by findings of animal

toxicological studies. Long-term exposure to $PM_{2.5}$ resulted in oxidative stress, inflammation, and morphologic changes in both upper and lower airways (Section 5.2.8), in addition to the asthma-related and lung development-related effects mentioned above. Epidemiologic studies examining the effects of declining $PM_{2.5}$ concentrations provide additional support for a relationship between long-term $PM_{2.5}$ exposure and respiratory health by demonstrating improvements in lung function growth and bronchitic symptoms in children and improvement in lung function in adults in association with declining $PM_{2.5}$ concentrations (Section 5.2.11). However, the limited examination of copollutant confounding in studies of declining $PM_{2.5}$ concentrations is a notable uncertainty given the corresponding decline in other pollutants over the time-period of the evaluated studies.

1.4.1.2 Cardiovascular Effects

Consistent with the conclusions of the 2009 PM ISA, more recently published scientific evidence further strengthens that there is a "*causal relationship*" between both short- and long-term $PM_{2.5}$ exposure and cardiovascular effects. These causality determinations are based on the consistency of findings within disciplines, coherence among evidence from controlled human exposure, epidemiologic, and toxicological studies, and biological plausibility for cardiovascular effects, such as reduced myocardial blood flow, altered vascular reactivity, myocardial infarctions, and cardiovascular mortality.

1.4.1.2.1 Cardiovascular Effects Associated with Short-Term $PM_{2.5}$ Exposure

Strong evidence from epidemiologic studies demonstrating associations between cardiovascular emergency department visits and hospital admissions in combination with evidence for $PM_{2.5}$-induced cardiovascular effects from controlled human exposure and animal toxicological studies confirms and extends the conclusion of a "*causal relationship*" between short-term $PM_{2.5}$ exposure and cardiovascular effects from the 2009 PM ISA (Table 1-2). This conclusion is based on multiple high-quality epidemiologic studies demonstrating associations with cardiovascular effects such as ischemic heart disease (IHD) and heart failure (HF) related emergency department visits and hospital admissions, as well as cardiovascular mortality. The epidemiologic evidence is primarily supported by experimental studies demonstrating endothelial dysfunction, changes in blood pressure, and alterations in heart function in response to short-term $PM_{2.5}$ exposure. Additional evidence from epidemiologic, controlled human exposure, and animal toxicological studies also provides ample evidence of biologically plausible pathways by which short-term exposure to $PM_{2.5}$ can result in overt cardiovascular effects.

Consistent with the 2009 PM ISA, the strongest evidence comes from epidemiologic studies that reported consistent positive associations between short-term $PM_{2.5}$ exposure and cardiovascular-related emergency department visits and hospital admissions particularly for IHD and HF, as well as cardiovascular-related mortality. While the evidence is generally consistent across the copollutants

evaluated, the evidence was especially consistent for air pollutants that are not typically associated with traffic (i.e., ozone, SO_2, $PM_{10-2.5}$). In some instances, associations in copollutant models were attenuated, but this was only observed for the traffic-related pollutants (i.e., NO_2, CO), which generally had higher correlations with $PM_{2.5}$ than other copollutants. This recent evidence generally indicates that the associations observed with $PM_{2.5}$ and cardiovascular effects in single pollutant models remain relatively unchanged in copollutant models, indicating that the observed associations with $PM_{2.5}$ are not artefacts due to confounding by another air pollutant (Section 6.1.14.1). These epidemiologic studies reduce a key uncertainty identified in the 2009 PM ISA by providing evidence that gaseous pollutants are not likely to confound the $PM_{2.5}$-cardiovascular relationship.

The independence of $PM_{2.5}$ effects is further addressed by findings of recent controlled human exposure and animal toxicological studies. The most consistent evidence from controlled human exposure studies is for a $PM_{2.5}$ effect on endothelial function. More specifically, in contrast to the previous review where a single controlled human exposure study did not find changes in endothelial function following short-term $PM_{2.5}$ exposure, multiple recent controlled human exposure studies that examined endothelial function reported that $PM_{2.5}$ impaired at least some measure of vessel dilation following reactive hyperemia or pharmacological challenge relative to filtered air exposure. Given the relationship between endothelial function and blood pressure, these results are coherent with controlled human exposure studies that reported changes in blood pressure following short-term $PM_{2.5}$ exposure. The results of these controlled human exposure studies are also coherent with evidence from animal toxicological studies demonstrating endothelial dysfunction and changes in blood pressure or the renin angiotensin system following short-term $PM_{2.5}$ exposure. Moreover, changes in endothelial function and blood pressure reported in experimental studies are consistent with time-series and case-crossover epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and IHD, as well as with limited epidemiologic panel study evidence of associations with blood pressure. In addition, animal toxicological studies demonstrating that short-term $PM_{2.5}$ exposure results in decreased cardiac contractility and left ventricular pressure are coherent with epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and HF.

Collectively, the evidence from controlled human exposure, animal toxicological and epidemiologic panel studies provide a biologically plausible pathway by which short-term $PM_{2.5}$ exposure could result in cardiovascular effects such as an emergency department visits, hospital admission, or mortality. This proposed pathway (Section 6.1.1) begins with pulmonary inflammation and/or activation of sensory nerves in the respiratory track. It progresses to autonomic nervous system imbalance and/or systemic inflammation that can potentially affect cardiovascular endpoints such as endothelial function, HRV, hemostasis, and/or BP. Changes in the aforementioned cardiovascular endpoints may then lead to the development of arrhythmia, thrombosis, and/or acute myocardial ischemia, potentially resulting in outcomes such as myocardial infarction, IHD, HF, and possibly death.

Overall, across the scientific disciplines, recent studies extend and support the previous evidence for a continuum of cardiovascular-related health effects following short-term exposure to $PM_{2.5}$. These effects range from relatively modest increases in biomarkers related to inflammation, to subclinical cardiovascular endpoints such as endothelial dysfunction, the overt outcomes of emergency department visits and hospital admissions, specifically for IHD and HF, and ultimately cardiovascular-related mortality.

1.4.1.2.2 Cardiovascular Effects Associated with Long-Term $PM_{2.5}$ Exposure

Multiple recent and previously available epidemiologic studies that extensively control for potential confounders provide strong evidence of positive associations with cardiovascular mortality, which in combination with supporting evidence from recent studies examining cardiovascular morbidity reaffirms the conclusion of a "*causal relationship*" between long-term $PM_{2.5}$ exposure and cardiovascular effects in the 2009 PM ISA (Table 1-2). This conclusion is based on recent U.S. and Canadian cohort studies demonstrating consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality with more limited evidence from studies examining long-term $PM_{2.5}$ exposure and cardiovascular morbidity.

Epidemiologic studies consisting of U.S.-based cohorts and subsequent analyses of these cohorts, provided the basis of the conclusions in the 2009 PM ISA. These studies in combination with recent cohort studies, continue to demonstrate consistent, positive associations and support a strong relationship between long-term $PM_{2.5}$ exposure and cardiovascular mortality. The results of these recent cohort studies are consistent across various spatial extents, exposure assessment techniques, and statistical techniques in locations where mean annual average concentrations are near or below 12 $\mu g/m^3$ (Section 6.2.10).

The body of literature examining the relationship between long-term $PM_{2.5}$ exposure and cardiovascular morbidity has greatly expanded since the 2009 PM ISA. Recent epidemiologic studies examining cardiovascular morbidity endpoints consist of several large U.S. cohort studies each focusing on populations with distinct demographic characteristics (e.g., post-menopausal woman, male doctors, etc.) and extensive consideration of potential confounders. These studies have reported heterogeneous results, with several high-quality studies that adjusted for important covariates, including socioeconomic status (SES), reporting positive associations for cardiovascular morbidity endpoints. The strong associations reported between long-term $PM_{2.5}$ exposure and coronary events (e.g., coronary heart disease [CHD] and stroke) among post-menopausal women in the Women's Health Initiative (WHI) cohort, highlighted in 2009 PM ISA, were strengthened in an extended analysis that considered individual and neighborhood level SES. Recent analyses of other cohorts of women (i.e., Nurses' Health Study, California Teachers Study) that were comparable to WHI in that they considered menopausal status or hormone replacement therapy did not show consistent positive associations with CHD, myocardial infarction or stroke. Longitudinal studies demonstrated that changes in the progression of atherosclerosis

in relation to long-term exposure to $PM_{2.5}$ were variable across cohorts and found to depend, in part, on the vascular bed in which atherosclerosis was evaluated. However, within a study focusing on the progression of atherosclerosis in a healthy population, i.e., Multi-Ethnic Study of Arthrosclerosis and Air Pollution (MESA-Air), an association was observed between long-term $PM_{2.5}$ exposure and coronary artery calcification (CAC), which is a strong predictor of CHD (Section 6.3.4). A small number of studies report positive associations between long-term $PM_{2.5}$ exposure and HF, blood pressure and hypertension. Longitudinal epidemiologic analyses also support the observation of positive associations with markers of systemic inflammation, coagulation and endothelial dysfunction. These HF studies are coherent with animal toxicological studies demonstrating decreased contractility and cardiac output, and increased coronary artery wall thickness following long-term $PM_{2.5}$ exposure (Section 6.2.4.2). Moreover, animal toxicological studies finding a relationship between long-term exposure to $PM_{2.5}$ and changes in BP in rats and mice are coherent with epidemiologic studies reporting positive associations between long-term exposure to $PM_{2.5}$ and hypertension. Similarly, evidence of atherosclerotic plaque progression in a genetically susceptible mouse model is consistent with epidemiologic studies reporting associations between atherosclerosis and long-term $PM_{2.5}$ exposure.

The current body of evidence also reduces uncertainties identified in the 2009 PM ISA related to potential copollutant confounding and the shape of the concentration-response relationship for CVD effects following long-term $PM_{2.5}$ exposure. Generally, most of the $PM_{2.5}$ effect estimates relating long-term $PM_{2.5}$ exposure and cardiovascular mortality remained relatively unchanged or increased in copollutant models adjusted for O_3, NO_2, SO_2, and $PM_{10-2.5}$ (Section 6.2.15). In addition, most of the results from analyses examining the C-R function for cardiovascular mortality supported a linear, no-threshold relationship for cardiovascular mortality, especially at mean annual $PM_{2.5}$ concentrations ≤ 12 $\mu g/m^3$ (Section 6.2.10). Some studies reported that the slope of the concentration-response function tended to be steeper at lower concentrations, especially for IHD mortality, suggesting a supralinear concentration-response relationship. A limited number of cardiovascular morbidity studies examined the shape of the concentration-response relationship and generally reported steeper concentration-response functions at lower concentrations (starting at ~10 $\mu g/m^3$) with the slope of the concentration-response function decreasing at higher $PM_{2.5}$ concentrations (Section 6.2.16).

Evidence from animal toxicological and epidemiologic studies also provide biologically plausible pathways by which long-term $PM_{2.5}$ exposure could lead to cardiovascular effect such as CHD, stroke, and CVD-related mortality (Section 6.2.1). These pathways initially involve autonomic nervous system changes and/or systemic inflammation that can potentially effect endpoints related to vascular function, altered hemostasis, hypertension, atherosclerotic plaque progression, and arrhythmia. Changes in cardiovascular endpoints such as these may then lead to IHD, HF, and possibly death.

Overall, there is consistent evidence from multiple, high-quality epidemiologic studies that long-term exposure to $PM_{2.5}$ is associated with cardiovascular mortality. Associations with CHD, stroke and atherosclerosis progression were observed in several recent high-quality epidemiologic studies